REMARKS

Claims 37-41 and 44-106 are in the application. Claims 1 to 39, 42 and 43 have been cancelled. Claims 37-41 have been amended. Claims 44-106 have been added. Support for the amendments and newly added claims lie in the working examples, the claims as originally filed in the PCT application, or in the specification on pages 7-13. No new matter is believed added.

Claims Calculation:
1-43 were submitted and paid for upon national stage entry, along with payment for 4 independent claims. In the claims as amended only 2 independent claims remain, 38 claims were cancelled, and 26 claims have been added (26 dependent claims X $18.00 = $460.00). Therefore, the Commissioner is hereby authorized to charge Deposit account 19-2570 for the additional claim fees of $460.00 necessitated by this if any additional fees or charges are required by this paper the Commissioner is hereby authorized to charge the Deposit account accordingly.

I. Rejection of Claims Based on Non-Statutory Obviousness-Type Double Patenting

Claim 1-3 and 7-14 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-8, 26-28, 108-110 and 118-120 of Applicant's copending Application No. 10/060,603. Applicants respectfully traverse this rejection.

Applicant's USSN 10/060,603 application is directed to the use of an entirely different copolymer, having a differing release rate characteristic in the patients gastro-intestinal environment than that of the present invention. The USSN 10/060,603 application uses a polymer, Eudragit E100 (also referred to as Aminoalkyl Methacrylate Copolymer E), which is a cationic copolymer. As noted on page 6 of the specification:

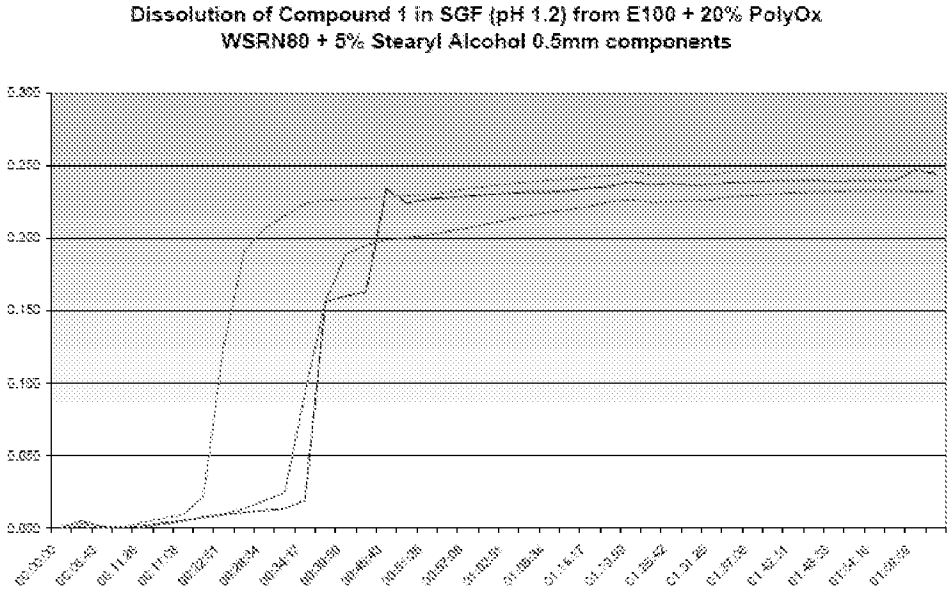
> "The polymer Eudragit 4135F™ dissolves only above pH 7, e.g. in the colon and so is suitable for formulation as a sustained release component. In contrast, the polymer Eudragit E100™ dissolves in acid as so is suitable for use as an immediate release component."

In contrast, the present invention is directed to the use of the polymer Eudragit 4135F which when blended in accordance with the excipients herein produces an erodible, and pH-independent formulation with reproducible release times in the order of 2 hours+.

While those release times are significantly faster than the non-blended formulation (which is not injection moldable) they are significantly longer than those of the E100 formulations described in Applicants copending application.

The E100 formulations in the USSN 10/060,603 application produce capsule shells and solid matrix subunits that generally dissolve within a 17 to 34 minute window, immediately delivering the drug to the stomach contents, not as a controlled release mechanism potentially over a 2-12 hour window.

For instance, see Figure 2 below:



The USSN 10/060,603 application (as presently amended) requires at least one dissolution modifying excipient which is polyethylene oxide present in an amount of about 5 to about 30% w/w; and optionally a second dissolution modifying excipient. A copy of the current claims and last response are attached herewith for the Examiners review.

There is no disclosure, as the Examiner so notes in the present Office Action (page 3), in Applicant's copending application that teaches a mixture of two hydroxypropylcellulose (HPC) polymers as a dissolution modifying excipient.

The Examiner uses the Nishioka reference (US 5,861,173) to teach a combination of HPC polymers with "different viscosity levels to obtain the release profile desired". (See Office Action, page 3, 3rd ¶).

The Examiner also uses the Gidwani et al. reference (US 6,270,797) as teaching a combination of hydroxypropylcellulose polymers having different molecular weights. (See Office Action, page 3, 4th ¶).

The Examiner also uses the Li et al. reference (US 7,476,403) as teaching a combination of hydroxypropylcellulose polymers having different molecular weights. (See Office Action, page 3, 5th ¶).

The Nishioka, the Gidwani and the Li references all teach using differing molecular weights of hydroxypropylcellulose in a controlled release dosage form for a particular active agent, however they use the HPC's in a traditional manner for such modified dose release in a tablet core. The tablet matrix admixes these polymers (as adjusted together) as gel-forming substances homogenously with the particular active agent which delays the release rate of the agent in the intestinal tract of the patient.

This is in direct contrast to the release rate of the active agent contained in the compartment of a capsule being controlled by the characteristics of the polymer composition which make up the shell or solid matrix subunit itself. The secondary references must utilize lots of different excipients in addition to the HPC's to actually produce a tablet, all of which can interfere and cause reactions with active agent to in the tablet in order to adequately control the release rate of the active. This can include fillers, binders, lubricants, disintegrants, etc. all of which have the potential to cause degradation or interference with the active agent.

In the instant case the active ingredient, without any of these excipients, can be placed into the capsule containing compartment and released into the patient's gastrointestinal environment with differing release rates. The release rate of the drug is therefore predicated on the composition of the extruded and molded capsule shell component, not on additionally admixed excipients with the agent, thus reducing potential interactions and stability issues. Furthermore, the claims at hand require two capsule subunits, a drug-substance containing compartment capsule shell and a solid matrix unit (which acts as a closure or linker to another drug-substance containing compartment capsule shell).

This is well described in Applicant's specification on page 13:

> "A plurality of sub units, e.g. of the capsule compartments, solid sub-units, or combinations thereof may comprise the same or different polymer(s). For example each of a plurality of sub units, e.g. of

> capsule compartments, solid sub-units, or combinations thereof may comprise the same or different drug substance. For example each sub-unit may contain the same drug substance but release the contents into the gastro-intestinal tract of the patient at a different rate, at different times after administration to the patient or at different places in the patient's gastro-intestinal system. Alternatively each sub-unit may contain a different drug substance, each of which may be released at the same or a different rate or time after administration or place in the patient's gastro-intestinal system.
>
> For example two or more sub-units, e.g. two capsule compartments, may each contain different drug substances, and/or different drug substance formulations, and/or the same drug in different formulations, so that a combination of two or more drug substances or formulations may be administered to a patient.
>
> The dosage form of this invention enables the assembly together of sub-units which differ in their drug content and/or drug content release characteristics to provide a dosage form tailored to specific administration requirements."

There is no teaching or suggestion in the secondary references that would motivate a skilled artisan to utilize differing molecular weight HPC's from a traditional modified release formulation to be used with a cationic polymer E100 composition and achieve the invention as claimed herein.

There is no teaching or suggestion in Applicants copending application that would suggest to the skilled artisan that the modification of the E100 copolymer would be capable of achieving longer controlled rates of release as in the Eudragit 4135F application. Lastly, there is no teaching or suggestion in Applicants copending application that would direct the skilled artisan to combine the 4135F polymer with more than one HPC of differing molecular weight to achieve consistent and reproducible release rates, nor that those release rates would be shorter than Applicants earlier filed 4135F applications USSN 10/060,849 and USSN 10/470,438

The Examiner's attention is directed to copending application USSN 10/895,588 which presently has a restriction in it to single component shells and subunits and the multi-component dosage forms as claimed herein. In view of the restriction therein, the claims of this national stage application (all stemming from the same provisional applications) have been amended in accordance with this restriction requirement.

It is unclear due to differing practice within Art Unit 1600 and the various group art units whether a terminal disclaimer or a priority claim under to that application is necessary. Applicants respectfully request a telephonic interview with the Examiner to discuss this matter more fully.

In view of these remarks, reconsideration and withdrawal of the rejection to the claims under the doctrine of obviousness-type double patenting are respectfully requested.

II. Rejection of Claims Under 35 U.S.C. §103(a)

Claims 1-43 are rejected as being unpatentable under 35 U.S.C. §103(a) over McAllister et al. (US2003/0049311) in view of Nishioka et al. (US 5,861,173) or Gidwani et al. (US 6,270,797) or Li et al. (US 7,476,403). Applicants respectfully traverse these rejections.

The McAllister et al. US 2003/0049311 reference corresponds to the above noted copending application of Applicants, USSN 10/060,603 in the obviousness type double patenting rejection.

For purposes of brevity, Applicants incorporate in its entirety their comments above from the obviousness type double patenting rejection.

Applicant's specification teaches that it is possible to have differing release rates of the contents of the capsule shells, and differing rates of release of the linker from the various capsule subunits. These differing release rates are determined by the polymeric composition that the capsule shells and subunits are composed of. The primary polymer along with the amounts of and types of excipients added to the polymer will determine whether the release will be immediate or delayed in some time from 'immediate' release. This is described throughout the specification

The polymeric composition of the present application, which is extruded and injection molded into the capsule shells or various capsule component subunits, such as a linker or end cap have a slower rate of release of the contents of the capsule compartment (or separation of the linker from the capsule component, etc., but a rate of release which is faster than a sustained or delayed release component. The present components also appear reproducibly the contents of the capsule compartment release, into the patients gastro-intestinal environment, in the order of 2 hours plus,

e.g. in the small intestines, as opposed to the stomach (gastric fluids) or with significant release delay into the colon.

It is not a simple matter to formulate any polymeric coating material, such as Eudragit E100 (as in the McAllister application) or the Eudragit 4135F polymer used herein as an extrudable and injection molded article of manufacture. The same excipients, if even present in a composition used for either coating tablets, or being incorporated into the matrix of a tablet core are not necessarily present in the same amounts for extrusion and injection molding. Too much lubricant in the formulations and the shells become to flexible and can not be clipped or welded together. Too little plasticizer and the shells can become brittle and crack. Nothing in the cited prior art provide the basis for the formulation as claimed, nor the processing /manufacturing steps as described herein.

The Examiner comments that "McAllister teaches the desirability for combing at least two dissolution (release) modifying agents" (See Office Action, page 7, 1rst line). Looking at paragraph 0147 in the McAllister application, the specific use of swellable solids, includes "polyethylene oxide, hydroxypropylmethylcellulose and other hydroxyalkylcellulose derivatives. Use of hydroxypropylcellulose has not been found to product suitable moldable capsule shells with E100 as the sole polymer. "

> [0147] More specifically, the class of agents known as swellable solids for use as dissolution modifying agents, includes but is not limited to poly(ethylene)oxide, hydroxypropylmethyl cellulose, and other hydroxyalkylcellulose derivatives. Use of hydroxypropylcellulose has not been found to produce suitable moldable capsule shells with E100 as the sole polymer. Suitably, the swellable solids used as dissolution modifying excipients are in the range of about 5% to about 60% w/w, preferably from about 5% to about 30% w/w.

However, that is what is specifically claimed for use herein. The polymer Eudragit 4135F may be extruded and molded using a blend of hydroxypropylcellulose polymers without the need for a secondary polymer. Consequently, the McAllister reference teaches away from the presently claimed invention.

It is an improper hindsight analysis to now combine the secondary references with the McAllister reference for the purposes of utilizing two HPC polymers of differing molecular weight. This is not withstanding the fact that the secondary references do not use the HPC polymers for same purpose as do Applicants.

Therefore even using the teaching, suggestion or motivation (TSM) test the skilled artisan would not be motivated to use the teachings of the McAllister reference alone or in combination with the secondary references to achieve the claimed invention herein. The Eudragit 4135F polymer is not taught in the McAllister reference. The use of hydroxypropylcellulose is not taught in the McAllister reference for use with a sole polymer (albeit it is the E100 polymer).

Even with KSR, there is no direction to pick a particular starting point(material) in McAllister for achieving an extruded and molded capsule subunit with a 2 hour + delay of release in the small intestines when the starting material in McAllister is an immediate release composition of a different copolymer.

There are many, different, available pathways available to the skilled artisan when looking at McAllister reference to produce a composition which has a different rate of release from that of the disclosed E100 polymer. The question to ask is why would one look to achieve a release rate that is 2 hours +, instead of 5+ hours plus, or even 10+ hours as a longer release rate than that of the E100 polymer? There is no reasonable prediction that could be made by the skilled artisan to make the necessary changes (as those herein) and know that such changes would produce a produce having the release characteristics that it does. In other words, there is no finite number of indentified and predictable solutions that face the skilled artisan in order to arrive at the claimed invention.

Looking at paragraphs 0129 -131 from the McAllister specification it is clear that there is no specific direction that would look to for obtaining a 2 hour + release rate from a molded component.

[0129] A preferred polymer is a material that preferentially dissolves or disintegrates at different points in the digestive tract. As noted above, such polymers include the known acrylic and/or methacrylic acid-based polymers, which are soluble in intestinal fluids, e.g. the Eudragit™ series of commercially available polymers. Examples of these include Eudragit E™, such as Eudragit E100™, which preferentially dissolves in the more acid pH of the stomach, or enteric polymers such as Eudragit L™ and/or Eudragit S™ which preferentially dissolve in the more alkaline pH of the intestine.

[0130] Other preferred polymers also include polymers which are insoluble but hydrate at a controlled rate, e.g. a predetermined rate in the digestive tract, such as Eudragit RL™, e.g. Eudragit RL 100™, and/or Eudragit RS™ e.g. Eudragit R100™, and/or blends of such Eudragit™ polymers. One such blend would be the combination of Eudragit RL and RS with the necessary glidants and excipients.

[0131] The polymer Eudragit 4135F™ dissolves only above pH 7, e.g. in the colon and so is suitable for formulation as a sustained release component. In contrast, as noted, the polymer Eudragit E100™ dissolves in acid so is suitable for use as an immediate release component.

Therefore, in view of these remarks and amendments, reconsideration and withdrawal of the rejection to the claims under 35 USC 103(a) are respectfully requested.

III. Rejection of Claims Under 35 U.S.C. §103(a)

Claims 1-43 are rejected as being unpatentable under 35 U.S.C. §103(a) over Brown et al. (WO 02/060384) in view of Nishioka et al. (US 5,861,173) or Gidwani et al. (US 6,270,797) or Li et al. (US 7,476,403). Applicants respectfully traverse these rejections.

Brown et al. (WO 02/060384) corresponds to copending application USSN 10/470,438 which is the national stage entry of the WO 02/060384 PCT application. Copending application USSN 10/060,849 also claims priority to the same provisional application as does USSN 10/470,438.

The Brown et al. application discloses use of swellable solids as a dissolution modifying excipient. The specification on page 28 states:

> "More specifically, the class of agents known as swellable solids for use as dissolution modifying agents, includes but is not limited to poly(ethylene)oxide, the cellulosic derivatives, such as ethyl cellulose and cellulose acetate phthalate; hydroxypropylcellulose (HPC), especially at lower molecular weights, e.g., KLUCEL EF and LF grades, available from Aqualon, hydroxypropylmethyl cellulose, and other hydroxyalkylcellulose

> derivatives. Suitably, the swellable solids used as dissolution modifying excipients are in the range of about 5% to about 70%w/w, preferably about 10 to 50%. Dependent upon whether an immediate or a longer dissolution rate profile is indicated, the amount of HPC, if so used, will vary. If an immediate dissolution rate is preferred than preferably there is about 40 to 70% w/w HPC present. If a modified pulse release rate profile is preferred, than the amount of HPC will be decreased, and suitably additional dissolution modifying excipients in combination with HPC will be used. Therefore the amount of HPC may vary from about 5 to 70% w/w. In combination, HPC is likely to present from 10 to 40% w/w, preferably <30% w/w."

Brown et al. does not, as the Examiner notes on page 7 of the Office action:

> "explicitly teach mixture of at least two HPC having differing MW. However, such combination is known in the art". not used in a manner which directs the skilled artisan to incorporate two HPC polymers in the matrix of an extruded and molded capsule shell component or solid matrix subunit.

Looking at Brown et al., the release rates is SIF fluid on page 45 vary from 2-9 to 11-18 hours (none of which include HPC). On page 46, when surfactants are added is also highly variable. Further examples with HPC, shown on pages 47-49 demonstrate more consistent and reproducible results but here the release rate is still much more delayed.

The Examiner then uses the secondary references, in particular Nishioka to teach a combination of HPC polymers to "obtain any release profile desired". However, as noted this is in a tablet matrix with a particular active ingredient homogenously embedded within the matrix. It is

Looking at page 48, the first full paragraph (below):

> "Additional formulation examples of the E 4135F polymer as a more delayed release shell component 6-8 hours (late-pulse) which contains an improved hydration response at pH>6 are shown below. In this particular grouping the E4135 is co-blended with hydroxypropylcellulose."

See first paragraph on page 49 below:

> "(Formulations for a delayed release/pulse (6-8 hours) containing a surfactant blend with Eudragit 4135F have also been produced using a APV 19mm extruder."

Brown et al teaches that incorporation of an HPC polymer (along with other excipients, and specifically a surfactant) can produce a consistent reliably reproducible component which has delayed release of 6-8 hours. Brown does not teach nor suggest that reliable, reproducible components would be achieved at a 2+ plus release by simply incorporating a second HPC polymer.

The TSM test does not direct the skilled artisan to achieve this end. Using a KSR analysis, again, while the starting material may now be a composition which can be extruded and injection molded with a Eudragit 4135F polymer, and one molecular weight of HPC, there needs to be some starting point as to why one would look to make an injection molded component having a 2+ plus release rate. There are many polymers that could be modified to achieve this rate. There are many other excipients which might be added to the 4135F polymer but why these changes would specifically achieve a reliable, reproducible 2 + plus release rate is not known. There are many changes and many pathways which the skilled artisan could use to achieve this end. Incorporation of a second dissolution modifying excipient that is a swellable solid, let alone a second hydroxypropylcellulose of a differing molecular weight are not pathways which one is directed to make without an improper hindsight analysis.

Therefore, in view of these remarks and amendments, reconsideration and withdrawal of the rejection to the claims under 35 USC 103(a) are respectfully requested.

IV. Rejection of Claims Under 35 U.S.C. §112, second paragraph

Claims 1-43 are rejected under 35 USC §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regards as the invention. Applicants respectfully traverse this rejection.

The Examiner comments that the claims contain the trademark/trade name "Eudragit 4135F" or "Klucel". The term Eudragit 4135F is amended in Claim 1 to the term "a copolymer of methyl acrylate, methyl methacrylate and methacrylic acid, with a molecular weight of about 220,000 and a ratio of free carboxyl groups to ester groups of 1:10". Support for this term is found in the Manufacturer's data sheet, a copy of which accompanies this response.

Klucel and Nisso are tradenames for hydroxypropylcellulose. They are well described in the specification on pages 7 and 8 in the specification in terms of their underlying viscosity and molecular weight. The claims have been amended accordingly.

In view of these remarks and amendments, reconsideration and withdrawal of the rejection to the claims under 35 USC §112, second paragraph are respectfully requested.

CONCLUSION

It is believed that all the claims in the application should be in condition for allowance as of this response. Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. If any additional fees or charges are required by this paper the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,

/ /

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Mc Allister et al.	11 June 2009
Serial No.:	10/895,588	Group Art Unit No.: 1615
Filed:	21 July 2004	Examiner: H. S. Ahmed

For: PHARMACEUTICAL FORMULATION

Commissioner for Patents
P.O. Box 1450
Arlington, VA 22313-1450

AMENDMENT & RESPONSE

Sir:

In response to the Examiner's Action mailed 13 May 2009 having a shortened statutory period of thirty days, please enter the following Remarks and Amendments into the record.

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 19 of this paper.

AMENDMENTS TO THE CLAIMS

This listing of claims will replace all prior versions, and listings, of claims in the application:

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Currently amended) A capsule comprising a shell having an outer surface and an opposed inner surface, the inner surface defining at least in part a confined space for holding a drug substance, and the outer surface being exposed to a gastro-intestinal environment, or a solid generally cylindrical body having an outer surface, the outer surface being exposed to a gastro-intestinal environment the shell or cylindrical body being composed of an extruded material comprising a pharmaceutical composition comprising a copolymer of methyl acrylate, methyl methacrylate and methacrylic acid, with a molar ratio of monomer units of 7:3:1, present in an amount of about 15 to about 50% w/w; at least two hydroxypropyl cellulose (HPC) polymers, each having a differing molecular weight, present in a total amount of 30 % to about 70% w/w; a lubricant present in an amount of about 10% to about 25% w/w; at least one dissolution modifying excipient selected from a disintegrant, a swellable solid, a non-reducing sugar, a water soluble filler, wicking agent, or inorganic salt, in a combination or mixture thereof, present in an amount of about 2.5 % to about 70% w/w; a surfactant present in an amount of 0 to 10%, a plasticizer present in an amount of 0 to 10% w/w and/or a processing agent present in an amount of 0 to about 10% w/w, wherein the shell material between and including the inner and outer surfaces, and the cylindrical body are comprised of the extruded and injection molded material.

2. (Previously Presented) The shell or cylindrical body according to Claim 1 wherein the copolymer is present in an amount of about 15 to about 30% w/w.

3. (Previously Presented) The shell or cylindrical body according to Claim 1 which comprises a surfactant present in an amount of less than 5% w/w.

4. (Previously Presented) The shell or cylindrical body according to Claim 3 wherein the surfactant is sodium dodecyl sulphate or is a block copolymer of ethylene oxide and propylene oxide.

5. (Previously Presented) The shell or cylindrical body according to Claim 4 wherein the surfactant is sodium dodecyl sulphate is present in an amount of less than 2% w/w.

6. (Previously Presented) The shell or cylindrical body according to Claim 4 wherein the surfactant is a block copolymer of ethylene oxide and propylene oxide.

7. (Previously Presented) The shell or cylindrical body according to Claim 1 wherein the lubricant is present in an amount of about 10 to about 15 % w/w.

8. (Previously Presented) The shell or cylindrical body according to Claim 1 wherein the lubricant is stearyl alcohol, glycerol monostearate (GMS), talc, magnesium stearate, silicon dioxide, amorphous silicic acid, or fumed silica; or a combination or mixture thereof.

9. (Previously Presented) The shell or cylindrical body according to Claim 8 wherein the lubricant is stearyl alcohol.

10. (Previously Presented) The shell or cylindrical body according to Claim 9 wherein the stearyl alcohol is present from about 10 to about 15% w/w.

11. (Previously Presented) The shell or cylindrical body according to Claim 1 wherein the at least one dissolution modifying excipient is a disintegrant selected from sodium starch glycollate, croscarmellose sodium, crospovidone (cross-linked polyvinyl pyrrolidone), or copovidone; a swellable solid selected from polyvinylpyrollidone, ethyl cellulose, cellulose acetate phthalate, a third hydroxypropyl cellulose polymer, hydroxypropylmethyl cellulose, or hydroxypropylmethyl cellulose phthalate; a non-

reducing sugar selected from xylitol, or mannitol ; a water soluble filler selected from lactose, or starch; an inorganic salt which is sodium chloride; or a combination or mixture thereof.

12. (Previously Presented) The shell or cylindrical body according to Claim 1 wherein the at least one dissolution modifying excipient is a disintegrant selected from sodium starch glycollate, croscarmellose sodium, crospovidone (cross-linked polyvinyl pyrrolidone), or copovidone, or a combination or mixture thereof.

13. (Previously Presented) The shell or cylindrical body according to Claim 1 wherein the at least one dissolution modifying excipient is a swellable solid selected from polyvinyl pyrrolidone copovidone;-ethyl cellulose, cellulose acetate phthalate, hydroxypropylmethyl cellulose, or hydroxypropylmethyl cellulose phthalate, or a combination or mixture thereof.

14. (Previously Presented) The shell or cylindrical body according to Claim 1 wherein the at least one dissolution modifying excipient is present in an amount of about 5 to about 15% w/w.

15. (Previously Presented) The shell or cylindrical body according to Claim 1 wherein the plasticizer is triethyl citrate (TEC), tributyl citrate, acetyl triethyl citrate (ATEC), acetyl tributyl citrate (ATBC), dibutyl phthalate, dibutyl sebacate (DBS), diethyl phthalate, vinyl pyrrolidone glycol triacetate, polyethylene glycol, polyoxyethylene sorbitan monolaurate, propylene glycol, castor oil; or a combination or mixture thereof.

16. (Previously Presented) The shell or cylindrical body according to Claim 1 wherein the processing agent is talc.

17. (Previously Presented) The shell or cylindrical body according to Claim 16 wherein the processing agent is present in an amount of about 1 to about 5 % w/w.

18. (Previously Presented) The shell or cylindrical body according to Claim 1 which further comprises an absorption enhancer.

19. (Previously Presented) The shell or cylindrical body according to Claim 18 wherein the absorption enhancer is chitosan, lecithin, lectin, a sucrose fatty acid ester, Vitamin E-TPGS; or a combination or mixture thereof.

20. (Previously Presented) The shell or cylindrical body according to Claim 1 wherein the copolymer is present in an amount of about 15 to 25% w/w, the lubricant is stearyl alcohol, the dissolution modifying excipient is sodium starch glycolate, and the surfactant is sodium dodecyl sulfate or a block copolymer of ethylene oxide and propylene oxide.

21. (Previously Presented) The shell or cylindrical body according to Claim 1 wherein the at least two HPC polymers have a resulting molecular weight of about 30,000 to about 370,000.

22. (Previously Presented) The shell or cylindrical body according to Claim 1 wherein the at least two HPC polymers have a resulting molecular weight of about 50,000 to about 170,000.

23. (Previously Presented) The shell or cylindrical body according to Claim 1 wherein the at least two HPC polymers have a resulting molecular weight of about 80,000 to about 140,000.

24. (Previously Presented) The shell or cylindrical body according to Claim 1 wherein the at least two hydroxypropyl cellulose polymers are independently selected from Klucel EF, Klucel E, Klucel EXF, Klucel JF, Klucel LF, Klucel GF, Nisso HPC-L and Nisso HPC-M.

25. (Previously Presented) The shell or cylindrical body according to Claim 1 wherein the at least two hydroxypropyl cellulose polymers are Klucel EF and Klucel JF.

26. (Previously Presented) The shell or cylindrical body according to Claim 1 wherein the at least two hydroxypropyl cellulose polymers are Klucel JF and Klucel GF.

27. (Previously Presented) The shell or cylindrical body according to Claim 1 wherein the at least two hydroxypropyl cellulose polymers are Klucel EF and Klucel GF.

28. (Previously Presented) The shell or cylindrical body according to Claim 1 wherein the at least two hydroxypropyl cellulose polymers are present in equal w/w % amounts of each component.

29. (Previously Presented) The shell or cylindrical body according to Claim 1 wherein the at least two hydroxypropyl cellulose polymers are present in an amount of about 32% w/w of each polymer.

30. (Previously Presented) The shell or cylindrical body according to Claim 1 wherein the at least one dissolution modifying excipient includes a second dissolution modifying excipient which is a wicking agent.

31. (Previously Presented) The shell or cylindrical body according to Claim 30 wherein the wicking agent is lactose.

32. (Previously presented) A pharmaceutical composition for molded capsule shells or cylindrical bodies the capsule shell wall or cylindrical body comprising:

Component	----------%w/w----------				
	A	or	B	or	C
Eudragit 4135F	24.0		24.0		24.0
Stearyl alcohol	12.0		12.0		12.0
Klucel EF	30.0		30.0		0.0

Klucel JF	30.0	0.0	30.0
Klucel GF	0.0	30.0	30.0
sodium starch glycollate:	2.0	2.0	2.0
sodium dodecyl sulfate	1.0	1.0	1.0
polyoxypropylene-polyoxyethylene block copolymers	1.0	1.0	1.0
Total	100	100	100 .

33. (Previously presented) A pharmaceutical composition for molded capsule shells or cylindrical bodies the capsule shell wall or cylindrical body comprising:

Component	----------% w/w----------		
	A or	B or	C
Eudragit 4135F	24.0	29.0	21.0
Stearyl alcohol	12.0	12.0	12.0
Klucel EF	32.0	25.0	32.0
Klucel JF	32.0	30.0	32.0
sodium starch glycollate:	0.0	2.0	2.0
sodium dodecyl sulfate	0.0	1.0	0.0
polyoxypropylene-polyoxyethylene block copolymers	0.0	1.0	1.0
Total	100	100	100 .

34. (Cancelled)

35. (Previously presented) A multicomponent injection molded capsule shell, and cylindrical body having a composition as defined in Claim 1.

36. (Previously presented) A welded multicomponent injection molded capsule shell, and cylindrical body having a composition as defined in Claim 1.

37. (Withdrawn) A multi-component pharmaceutical dosage form which comprises a plurality of sub-units, each sub-unit being selected from

a) a drug substance-containing capsule compartment comprising a shell having an outer surface and an opposed inner surface, the inner surface defining at least in part a confined space for holding a drug substance, and the outer surface being exposed to a gastro-intestinal environment which is soluble or disintegrable in a patient's gastro-intestinal environment for release of the drug substance contained in the capsule compartment, and wherein the shell is composed of an extruded material comprising a pharmaceutical composition comprising a copolymer of methyl acrylate, methyl methacrylate and methacrylic acid, with a molar ratio of monomer units of 7:3:1, present in an amount of about 20 to about 40 % w/w, at least two hydroxypropyl cellulose polymers, each having a differing molecular weight being present in a total amount of about 30 % to about 70 % w/w, a lubricant present in an amount of about 10% to about 25% w/w; at least one dissolution modifying excipient selected from a disintegrant, a swellable solid, a non-reducing sugar, a water soluble filler, wicking agent, or inorganic salt, in a combination or mixture thereof, present in an amount of about 0% to about 70% w/w; a surfactant present in an amount of 0 to 10%, a plasticizer present in an amount of 0 to 10% w/w and/or a processing agent present in an amount of 0 to about 10% w/w, wherein the shell material between and including the inner and outer surfaces is comprised of the extruded material;

b) a solid generally cylindrical body having an outer surface, the outer surface being exposed to a gastro-intestinal environment the cylindrical body being composed on an extruded material comprising a pharmaceutical composition comprising a copolymer of methyl acrylate, methyl methacrylate and methacrylic acid, with a molar ratio of monomer units of 7:3:1, present in an amount of about 20 to about 40 %, at least two hydroxypropyl cellulose polymers, each having a differing molecular weight being present in a total amount of about 30 % to about 70 % w/w, a lubricant present in an amount of about 10% to about 25% w/w; at least one dissolution modifying excipient selected from a disintegrant, a swellable solid, a non-reducing sugar, a water soluble filler, wicking agent, or inorganic salt, in a combination or mixture thereof, present in an amount of about 0% to about 70% w/w; a surfactant present in an amount of 0 to 10%, a plasticizer present in an amount of 0 to 10% w/w and/or a processing agent present in an amount of 0 to about 10% w/w , and wherein the cylindrical body is comprised of the extruded material, containing a drug substance, the polymer being soluble, dispersible or disintegrable in a patient's gastro-intestinal environment for release of the drug substance

contained in the solid matrix, and in which, at least prior to administration to a patient, the sub-units are assembled together in a dosage form.

38. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 37, in which at least one of the capsule compartment subunits polymeric composition comprises as the hydroxypropylcellulose polymers, Klucel EF and Klucel JF, each present in an amount of about 30 to 32% w/w.

39. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 37, in which at least one of the capsule compartment subunits polymeric composition comprises as the hydroxypropylcellulose polymers, Klucel JF and Klucel GF, each present in an amount of about 30 to 32% w/w.

40. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 37, in which at least one of the capsule compartment subunits polymeric composition comprises as the hydroxypropylcellulose polymers, Klucel EF and Klucel GF, each present in an amount of about 30 to 32% w/w.

41. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 37, in which the polymeric composition also comprises a lubricant present in an amount of about 10 to about 25% w/w.

42. (Currently amended)(Withdrawn) A <u>multi-component pharmaceutical</u> dosage form according to Claim 37, in which at least one of the sub-units is a drug substance-containing capsule compartment having a wall with a thickness in the range of about 0.3 – 0.8 mm.

43. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 42, in which at least one of the sub-units releases the drug substance as a substantially immediate release.

44. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 41, wherein the lubricant is stearyl alcohol, glycerol monostearate (GMS), talc, magnesium stearate, silicon dioxide, amorphous silicic acid, or fumed silica; or a combination or mixture thereof.

45. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 44, wherein the lubricant is stearyl alcohol.

46. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 45, wherein the stearyl alcohol is present from about 10 to about 15% w/w.

47. (Cancelled)

48. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 37, wherein the at least one dissolution modifying excipient is a disintegrant selected from sodium starch glycollate, croscarmellose sodium, crospovidone (cross-linked polyvinyl pyrrolidone), or copovidone; a swellable solid selected from polyvinylpyrollidone, ethyl cellulose, cellulose acetate phthalate, a third hydroxypropyl cellulose polymer, hydroxypropylmethyl cellulose, or hydroxypropylmethyl cellulose phthalate; a non-reducing sugar selected from xylitol, or mannitol; a water soluble filler selected from lactose, or starch; an inorganic salt which is sodium chloride; or a combination or mixture thereof.

49. (Currently amended) (Withdrawn) A multi-component pharmaceutical dosage form according to Claim [[47]] 37, wherein the at least one dissolution modifying excipient is a disintegrant selected from sodium starch glycollate, croscarmellose sodium, crospovidone (cross-linked polyvinyl pyrrolidone), or copovidone, or a combination or mixture thereof.

50. (Currently amended) (Withdrawn) A multi-component pharmaceutical dosage form according to Claim [[47]] 37, wherein the at least one dissolution modifying excipient is a swellable solid selected from polyvinyl pyrrolidone copovidone; ethyl cellulose, cellulose acetate phthalate, hydroxypropylmethyl cellulose, or hydroxypropylmethyl cellulose phthalate,-or a combination or mixture thereof.

51. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 48 , herein the dissolution modifying excipient is present in an amount of about 5 to about 15% w/w.

52.(Cancelled)

53.(Withdrawn) A multi-component pharmaceutical dosage form according to Claim 37, wherein the plasticizer is selected from the group consisting of triethyl citrate (TEC), tributyl citrate, acetyl triethyl citrate (ATEC), acetyl tributyl citrate (ATBC), dibutyl phthalate, dibutyl sebacate (DBS), diethyl phthalate, vinyl pyrrolidone glycol triacetate, polyethylene glycol, polyoxyethylene sorbitan monolaurate, propylene glycol, and castor oil; and combinations or mixtures thereof.

54. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 37, wherein the processing agent is talc.

55. (Cancelled)

56. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 37 wherein the surfactant is sodium dodecyl sulphate or is a block copolymer of ethylene oxide and propylene oxide.

57. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 56, wherein the surfactant is present in an amount of less than 5% w/w.

58. (Withdrawn) A multi-component pharmaceutical dosage form which comprises a plurality of sub-units, each sub-unit being selected from

a) a drug substance-containing capsule compartment comprising a shell having an outer surface and an opposed inner surface, the inner surface defining at least in part a confined space for holding a drug substance, and the outer surface being exposed to a gastro-intestinal environment which is soluble or disintegrable in a patient's gastro-

intestinal environment for release of the drug substance contained in the capsule compartment, and wherein the shell is composed of an extruded material comprising pharmaceutical composition comprising a copolymer of methyl acrylate, methyl methacrylate and methacrylic acid, with a molar ratio of monomer units of 7:3:1, present in an amount of about 20 to 40% w/w, at least two hydroxypropyl cellulose polymers, each having a differing molecular weight being present in a total amount of about 30 % to about 70% w/w, a lubricant present in an amount of about 10% to about 15% w/w; at least one dissolution modifying excipient selected from a disintegrant, a swellable solid, a non-reducing sugar, a water soluble filler, wicking agent, or inorganic salt, in a combination or mixture thereof, present in an amount of about 0% to about 70% w/w, a surfactant present in an amount of 0 to 10%, a plasticizer present in an amount of 0 to 10% w/w and/or a processing agent present in an amount of 0 to about 10% w/w, and wherein the shell material between and including the inner and outer surfaces is comprised of the extruded material;

b) a solid generally cylindrical body having an outer surface, the outer surface being exposed to a gastro-intestinal environment the cylindrical body being composed on an extruded material comprising a pharmaceutical composition comprising a copolymer of methyl acrylate, methyl methacrylate and methacrylic acid, with a molar ratio of monomer units of 7:3:1, 20 to 40% w/w, at least two hydroxypropyl cellulose polymers, each having a differing molecular weight being present in a total amount of about 30 % to about 70% w/w, a lubricant present in an amount of about 10% to about 15% w/w; at least one dissolution modifying excipient selected from a disintegrant, a swellable solid, a non-reducing sugar, a water soluble filler, wicking agent, or inorganic salt, in a combination or mixture thereof, present in an amount of about 0% to about 70% w/w, a surfactant present in an amount of 0 to 10%, a plasticizer present in an amount of 0 to 10% w/w, and/or a processing agent present in an amount of 0 to about 10% w/w, and wherein the cylindrical body is comprised of the extruded material, and wherein prior to administration to a patient, the sub-units are assembled together in said dosage form.

59. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 58, in which at least one of the shell subunits polymeric composition comprises as the hydroxypropylcellulose polymers, Klucel EF and Klucel JF, each present in an amount of about 30 to 32% w/w.

60. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 58, in which at least one of the shell subunits polymeric composition comprises as the hydroxypropylcellulose polymers, Klucel JF and Klucel GF, each present in an amount of about 30 to 32% w/w.

61. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 58, in which at least one of the shell subunits polymeric composition comprises as the hydroxypropylcellulose polymers, Klucel EF and Klucel GF, each present in an amount of about 30 to 32% w/w.

62. to 63. (Cancelled)

64. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 58, in which at least one of the sub-units is a drug substance-containing capsule compartment having a shell wall with a thickness in the range of about 0.3 – 0.8 mm.

65. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 58, in which at least one of the drug substance-containing capsule compartment releases the drug substance as a substantially immediate release.

66. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 58, wherein the lubricant is stearyl alcohol.

67. ((Withdrawn) A multi-component pharmaceutical dosage form according to Claim 66, wherein the stearyl alcohol is present from about 10 to about 15% w/w.

68. (Currently amended)(Withdrawn) A multi-component pharmaceutical dosage form according to Claim 58, wherein the polymeric composition comprises at least one dissolution modifying excipient which is a disintegrant selected from sodium starch glycollate, croscarmellose sodium, crospovidone (cross-linked polyvinyl pyrrolidone), or copovidone [[,]] ; a swellable solid selected from polyvinylpyrollidone, ethyl cellulose, cellulose acetate phthalate, a third hydroxypropyl cellulose polymer, hydroxypropylmethyl cellulose, or hydroxypropylmethyl cellulose phthalate ; a non-reducing sugar selected from xylitol, or mannitol; a water soluble filler selected from

lactose, or starch; an inorganic salt which is sodium chloride; or a combination or mixture thereof.

69. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 68, wherein the at least one dissolution modifying excipient is a disintegrant selected from sodium starch glycollate, croscarmellose sodium, crospovidone (cross-linked polyvinyl pyrrolidone), or copovidone, or a combination or mixture thereof.

70. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 68, wherein the at least one dissolution modifying excipient is a swellable solid selected from polyvinyl pyrrolidone copovidone;-ethyl cellulose, cellulose acetate phthalate, hydroxypropylmethyl cellulose, or hydroxypropylmethyl cellulose phthalate, or a combination or mixture thereof.

71. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 68, wherein the dissolution modifying excipient is present in an amount of about 5 to about 15% w/w.

72. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 58, wherein the plasticizer is selected from the group consisting of triethyl citrate (TEC), tributyl citrate, acetyl triethyl citrate (ATEC), acetyl tributyl citrate (ATBC), dibutyl phthalate, dibutyl sebacate (DBS), diethyl phthalate, vinyl pyrrolidone glycol triacetate, polyethylene glycol, polyoxyethylene sorbitan monolaurate, propylene glycol, and castor oil; and combinations or mixtures thereof.

73. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 72, wherein the processing agent is talc.

74. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 58, wherein the surfactant is sodium dodecyl sulphate or is a block copolymer of ethylene oxide and propylene oxide.

75. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 74, wherein the surfactant is present in an amount of less than 5% w/w.

76. (Previously Presented) The shell or cylindrical body according to Claim 1 wherein the at least one dissolution modifying excipient is a water soluble filler selected from lactose or starch and is present in an amount of about 5 to about 20% w/w.

77. (Previously Presented) The shell or cylindrical body according to Claim 1 wherein the at least one dissolution modifying excipient is a non-reducing sugar selected from xylitol, or mannitol and is present in an amount of about 2.5 to about 15% w/w.

78. (Previously Presented) The shell or cylindrical body according to Claim 13 wherein the at least one dissolution modifying excipient is present in an amount of about 10 to about 40% w/w.

79. (Previously Presented) The shell or cylindrical body according to Claim 78 wherein the at least one dissolution modifying excipient is present in an amount of about 20 to about 30% w/w.

80. (Previously Presented) The shell or cylindrical body according to Claim 13 wherein the at least one dissolution modifying excipient is present in an amount of about 5 to about 70% w/w.

81. (Previously Presented) The shell or cylindrical body according to Claim 1 wherein the lubricant is stearyl alcohol present in an amount of about 10 to about 15% w/w, and the at least one dissolution modifying excipient is a disintegrant, and a surfactant which is sodium dodecyl sulfate or a block copolymer of ethylene oxide and propylene oxide.

82. (Previously Presented) The shell or cylindrical body according to Claim 81 wherein the disintegrant is sodium starch glycollate or croscarmellose sodium present in about 10% w/w of the formulation.

83 (Previously Presented) The shell or cylindrical body according to Claim 1 wherein the at least one dissolution modifying excipient is a swellable solid selected from ethyl cellulose, cellulose acetate phthalate, or hydroxypropylmethyl cellulose phthalate, and combinations or mixtures thereof.

84. (Previously Presented) A capsule comprising a shell having an outer surface and an opposed inner surface, the inner surface defining at least in part a confined space for holding a drug substance, and the outer surface being exposed to a gastro-intestinal environment; or a solid generally cylindrical body having an outer surface, the outer surface being exposed to a gastro-intestinal environment the shell or cylindrical body being composed of an extruded material comprising;

a pharmaceutical composition comprising a copolymer of methyl acrylate, methyl methacrylate and methacrylic acid, with a molar ratio of monomer units of 7:3:1, present in an amount of about 15 to about 30% w/w; at least two hydroxypropyl cellulose (HPC) polymers, each having a differing molecular weight, present in a total amount of 30 % to about 70% w/w; a lubricant which is stearyl alcohol present in an amount of about 10% to about 15% w/w; at least one dissolution modifying excipient selected from a disintegrant, a non-reducing sugar, a water soluble filler, wicking agent, or an inorganic salt, in a combination or mixture thereof, present in an amount of about 2.5 % to about 15% w/w; a surfactant present in an amount of 0 to 10%, a plasticizer present in an amount of 0 to 10% w/w and/or a processing agent present in an amount of 0 to about 10% w/w, wherein the shell material between and including the inner and outer surfaces, and the cylindrical body are comprised of the extruded material.

85 (Previously Presented) The shell or cylindrical body according to Claim 84 which comprises a second dissolution modifying excipient which is a swellable solid.

86 (Previously Presented) The shell or cylindrical body according to Claim 85 which comprises a second dissolution modifying excipient which is a third hydroxypropyl cellulose (HPC) polymer.

87 (Previously Presented) The shell or cylindrical body according to Claim 85 which comprises a second dissolution modifying excipient which is hydroxypropyl methyl cellulose.

88. (Previously Presented) The shell or cylindrical body according to Claim 85 wherein the swellable solid selected from polyvinyl pyrrolidone, ethyl cellulose, cellulose acetate phthalate, hydroxypropylmethyl cellulose, or hydroxypropylmethyl cellulose phthalate, or a combination or mixture thereof.

89. (Previously Presented) The shell or cylindrical body according to Claim 84 wherein the plasticizer is triethyl citrate (TEC), tributyl citrate, acetyl triethyl citrate (ATEC), acetyl tributyl citrate (ATBC), dibutyl phthalate, dibutyl sebacate (DBS), diethyl phthalate, vinyl pyrrolidone glycol triacetate, polyethylene glycol, polyoxyethylene sorbitan monolaurate, propylene glycol, castor oil; or a combination or mixture thereof.

90. (Previously Presented) The shell or cylindrical body according to Claim 84 wherein the processing agent is talc.

91. (Currently amended) (withdrawn) A multi-component pharmaceutical dosage form [[The shell or cylindrical body]] according to Claim 37 wherein the at least one dissolution modifying excipient is a water soluble filler selected from lactose or starch and is present in an amount of about 5 to about 20% w/w.

92. (Currently amended) (withdrawn) A multi-component pharmaceutical dosage form [[The shell or cylindrical body]] according to Claim 37 wherein the at least one

dissolution modifying excipient is a non-reducing sugar selected from xylitol, or mannitol and is present in an amount of about 2.5 to about 15% w/w.

93. (Currently amended) (withdrawn) A multi-component pharmaceutical dosage form [[The shell or cylindrical body]] according to Claim 58 wherein the at least one dissolution modifying excipient is a water soluble filler selected from lactose or starch and is present in an amount of about 5 to about 20% w/w.

94. (Currently amended) (withdrawn) A multi-component pharmaceutical dosage form [[The shell or cylindrical body]] according to Claim 58 wherein the at least one dissolution modifying excipient is a non-reducing sugar selected from xylitol, or mannitol and is present in an amount of about 2.5 to about 15% w/w.

REMARKS

In response to Examiner's Office Action of 13 May 2009, a restriction under 35 USC § 121 has been required.

Claims 1 to 33, 35 to 46, 48 to 51, 53, 54, 56, 57 and 76 to 94 are in the application. Claim 34 has been cancelled. Claims 1, 42, 49, 50 and 91-94 has been amended. Claim 34 has been incorporated into Claim 1. Claims 42 and 91-94 correct the preamble of the claim. The claim dependency of claims 49 and 50 has been corrected. No new matter is believed added.

Claims 1-36, and 76-90 drawn to capsule shells or cylindrical bodies are classified in 424/489.

Claims 37-46, 48-51, 53, 54, 56-61, 64-75 and 91-94 are drawn to multicomponent pharmaceutical dosage forms, also classified in 424/489.

Applicants respectfully traverse this restriction requirement.

A review of the MPEP Classification Manuel indicates that Class 424 covers Drug, Bio-affecting and body treating compositions, and that subclass 489 is directed to:

489. **Particulate form (e.g., powders, granules, beads, microcapsules, and pellets):** This subclass is indented under subclass 400. Subject matter in which the special physical form is a coated or impregnated particle.

(1) Note. Particle is intended to encompass any form which is solid but of sufficiently small size to behave in a fluid manner.

(2) Note. This subclass includes any form denominated as powder, granule, bead, microcapsule or pellet.

The articles of manufacture herein appear to be improperly classified within this subclass. They are not powders, granules, bead, microcapsules or pellets. The invention is not a composition which is a "drug". The invention is directed to a capsule shell or linker or other subunit which is comprised of a pharmaceutical composition that have been injection molded into a dosage form.

The Examiners basis for this restriction is that "the intermediate product is deemed to be useful as an outer layer for a single-component dosage form, and the inventions are deemed patentably distinct because there is nothing of record to show them to be obvious variants.

It is unclear what the Examiner is actually stating as the basis of the restriction. What is "to be useful as an outer layer for a single-component dosage form" mean?

The composition is not an outer layer applied to an existing dosage form, it is the dosage form. The only difference between these 2 groups is the in Group I it is the individual component which is being claimed and in Group II it is the final dosage form. Therefore all the attributes of Group I must also be examined with Group II and vice versa. The multicomponent dosage form is simply the end result of a common R&D effort for injection molding the capsule shells, linker and other subunits of this invention.

This application has been pending since July 2004. The claims of the application have had at least 4 office actions since filing. Within the context of this prior examination a terminal disclaimer has been filed.

The Examiner comments that this restriction is necessary "in view of applicants' newly added claims". However, the newly added claims are only dependent claims to those which have already been filed and examined previously.

Applicants elect Group I with traverse based upon the comments above.

An election of species is requested by the Examiner, with election of a particular surfactant, a dissolution modifying agents and an HPC combination of claims 25, 26, or 27. The Examiner further request election of a formulation (a or b) from that of claims 32 and 33. This is inconsistent with the previous excipient election as an election of a particular lubricant has not been required (and is specific to that of claims 32 and 33) as is the inclusion or not of a disintegrant and a surfactant. For instance, Formulation A in claim 33 has none of these, where as formulation B has all of them, etc. However, in order to advance prosecution Applicants elect claim 32 as representative of the compositions of claim 1 which are injection molded into suitable dosage forms.

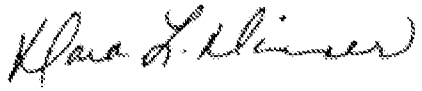
Lastly, the Examiner also requests an "election of a capsule shell type". Again this is inconsistent with the overall restriction. The subject matter of Claim 34 has been added to Claim 1. Claim 35 is concerned with multiple units of the components as defined in claim 1 and Claim 36 simply requires that both the capsule shell and the cylindrical body having a composition according to Claim 1 (e.g. multiple units) are welded together. Applicants elect claim 35.

Applicants further elect SDS as a surfactant, a disintegrant as the at least one dissolution modifying excipient, and the combination of two differing hydroxypropylcellulose derivatives as Claim 25.

All of the claims directed to the capsule shell or cylindrical body except for claims 5, 13, 26, 27, 76-78, 80, 83, 85-88 fall within the elected groups.

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. It is not believed that this paper should cause any additional fees or charges to be required, other than expressly provided for already. However, if this is not the case the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,



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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Mc Allister et al.	4 September 2009
Serial No.:	10/060,849	Group Art Unit No.: 1618
Filed:	30 January 2002	Examiner: S. Tran
For:	PHARMACEUTICAL FORMULATION	

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

RESPONSE & AMENDMENT

Dear Sir:

In response to the Examiner's Action mailed 4 March 2009, having a shortened statutory period of 3 months, entry of the following Remarks and Amendments into the record is respectfully requested. Enclosed herewith is a petition for a three (3) month extension of the shortened statutory period set by the Examiner and authorization to charge the required fee to the indicated deposit account.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 23 of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

1 (Currently amended). A capsule shell, having an outer surface and an opposed inner surface, the inner surface defining at least in part a confined space for holding a drug substance, and the outer surface being exposed to a gastro-intestinal environment, the capsule shell being composed of an extruded and injection molded capsule shell composition comprising:

a copolymer of methyl acrylate, methyl methacrylate and methacrylic acid with a molar ratio of monomer units represented as 7:3:1, and a ratio of free carboxyl groups to esters groups of 1:10, present in an amount of about 20 to 90% w/w;

a lubricant present in an amount of 5 to about 30% w/w;

a combination of dissolution modifying excipients present in an amount of about 2.5 to about 70% w/w, and wherein each one of the dissolution modifying agents is selected from the group consisting of a swellable solid present in the range of about 5% to about 70%w/w, a non-reducing sugar present in the range of about 2.5 to 15% w/w; a water soluble filler present in the range of about 5 to 20%, a wicking agent present in the range of 5-10%, and a disintegrant present in the range of about 10 to 40%; and

optionally a surfactant present in an amount of 0 to 10%, a plasticizer present in the amount of 0 to 10% w/w and/or a processing agent present in an amount of 0 to about 10% w/w;

wherein the extruded capsule shell composition is substantially pH-independent.

2. (Previously presented) The capsule shell composition according to Claim 1 wherein the copolymer is present in an amount of about 50 to 90% w/w.

3. (Previously presented) The capsule shell composition according to Claim 1 which comprises a surfactant which is present in an amount of less than 5% w/w.

4. (Previously presented) The capsule shell composition according to Claim 3 wherein the surfactant is sodium dodecyl sulphate or is a block copolymer of ethylene oxide and propylene oxide.

5. (Previously presented) The capsule shell composition according to Claim 4 wherein the surfactant is sodium dodecyl sulphate is present in an amount of less than 2% w/w.

6. (Previously presented) The capsule shell composition according to Claim 4 wherein the surfactant is a block copolymer of ethylene oxide and propylene oxide.

7. (Previously presented) The capsule shell composition according to Claim 1 wherein the lubricant is present in an amount of about 10 to 25 % w/w.

8. (Previously presented) The capsule shell composition according to Claim 1 wherein the lubricant is stearyl alcohol, glycerol monostearate (GMS), talc, magnesium stearate, silicon dioxide, amorphous silicic acid, or fumed silica; and combinations or mixtures thereof.

9. (Previously presented) The capsule shell composition according to Claim 8 wherein the lubricant is stearyl alcohol.

10. (Previously presented) The capsule shell composition according to Claim 9 wherein the stearyl alcohol is present from about 10 to about 15% w/w.

11. (Currently amended) The capsule shell composition according to Claim 1 wherein the combination of dissolution modifying excipients contains at least one dissolution modifying excipient is a swellable solid which is ethyl cellulose, cellulose acetate phthalate; hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate, or other hydroxyalkylcellulose derivative; and combinations or mixtures thereof.

12. (Previously presented) The capsule shell composition according to Claim 11 wherein the at least one dissolution modifying excipient is hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate, or hydroxypropyl cellulose; and combinations or mixtures thereof.

13. (Previously presented) The capsule shell composition according to Claim 12 wherein the at least one dissolution modifying excipient is present in an amount of about 10 to 50% w/w.

14. (Currently amended) The capsule shell composition according to Claim 1 wherein the combination of dissolution modifying excipients contains at least one dissolution modifying excipient which is selected from xylitol, mannitol, lactose, pregelatinized starch, sodium chloride, sodium starch glycollate, croscarmellose sodium, crospovidone (cross-linked polyvinyl pyrrolidone), copovidone, or polyvinyl pyrrolidone, and combinations or mixtures thereof.

15. (Previously presented) The capsule shell composition according to Claim 14 wherein the at least one dissolution modifying excipient is present in an amount of about 40 to 70% w/w.

16. (Currently amended) The capsule shell composition according to Claim 11 wherein the at least one dissolution modifying excipient is a swellable solid and at least one other dissolution modifying excipient selected from lactose, sodium starch glycollate, croscarmellose sodium, copovidone, crospovidone (cross-linked polyvinyl pyrrolidone), or polyvinyl pyrrolidone.

17. (Previously presented) The capsule shell composition according to Claim 16 wherein the at least one dissolution modifying excipient is hydroxypropylcellulose and the at least one other dissolution modifying excipient is lactose.

18. (Previously presented) The capsule shell composition according to Claim 1 wherein the surfactant is a block copolymer of ethylene oxide and propylene oxide, lecithin, sodium dioctyl sulfosuccinate, sodium dodecyl sulphate, Polyoxyl 40 hydrogenated castor oil, polyoxyethylene sorbitan fatty acid esters, the sorbitan fatty acid esters, polyethylene glycol, Vitamin E-TPGS® (d-alpha-tocopheryl polyethylene glycol 1000 succinate), sucrose fatty acid ester; and combinations and mixtures thereof.

19. (Previously presented) The capsule shell composition according Claim 18 wherein the combination of dissolution modifying excipients is a combination of a swellable solid and lactose, sodium starch glycollate, croscarmellose sodium, copovidone, crospovidone (cross-linked polyvinyl pyrrolidone), or polyvinyl pyrrolidone.

20. (Previously presented) The capsule shell composition according to Claim 1 wherein the plasticizer is triethyl citrate (TEC), tributyl citrate, acetyl triethyl citrate (ATEC), acetyl tributyl citrate (ATBC), dibutyl phthalate, dibutyl sebacate (DBS), diethyl phthalate, vinyl pyrrolidone glycol triacetate, polyethylene glycol, polyoxyethylene sorbitan monolaurate, propylene glycol, or castor oil; and combinations or mixtures thereof.

21. (Previously presented) The capsule shell composition according to Claim 1 wherein the processing agent is talc.

22. (Previously presented) The capsule shell composition according to Claim 21 wherein the processing agent is present in an amount of about 1 to about 5 % w/w.

23. (Previously presented) The capsule shell composition according to Claim 1 which further comprises an absorption enhancer.

24. (Previously presented) The capsule shell composition according to Claim 23 wherein the absorption enhancer is chitosan, lecithin, lectin, a sucrose fatty acid ester, Vitamin E-TPGS; and combinations or mixtures thereof.

25. (Currently amended) The capsule shell composition according to Claim 1 wherein the copolymer is present in an amount of about 50 to 90% w/w, the lubricant is stearyl alcohol present in an amount of about 10 to about 15% w/w, and the combination of dissolution modifying excipients contains at least one dissolution modifying excipient which is hydroxypropylmethylcellulose, hydroxypropylcellulose, or a hydroxylalkyl cellulose derivative or salt thereof.

26. (Previously presented) The capsule shell composition according to Claim 25 wherein at least one other dissolution modifying excipient is a disintegrant.

27. (Previously presented) The capsule shell composition according to Claim 26 wherein the disintegrant is sodium starch glycollate, croscarmellose sodium, copovidone, crospovidone (cross-linked polyvinyl pyrrolidone), or polyvinyl pyrrolidone, or a combination or mixture thereof.

28. (Previously presented) The capsule shell composition according to Claim 25 wherein at least one other dissolution modifying excipient is a wicking agent.

29. (Previously presented) The capsule shell composition according to Claim 28 wherein the wicking agent is lactose.

30. (Previously presented) The capsule shell composition according to Claim 25 wherein the processing aid is talc.

31. (Previously presented) The capsule shell composition according to Claim 1 which is:

	Formulation	% w/w	
	Copolymer Stearyl alcohol Mannitol Sodium starch glycollate	75.0 5.0 10.0 10.0	or
	Copolymer Stearyl alcohol Mannitol Sodium starch glycollate	65.0 5.0 10.0 20.0	or
	Copolymer Stearyl alcohol Sodium starch glycollate Lactose monohydrate	80.0 5.0 10.0 5.0	or
	Copolymer Stearyl alcohol Sodium starch glycollate Lactose monohydrate	75.0 5.0 10.0 10.0	or
	Copolymer Stearyl alcohol Sodium starch glycollate Lactose monohydrate	80.0 5.0 5.0 10.0	or
	Copolymer Stearyl alcohol Sodium starch glycollate Lactose monohydrate	70.0 5.0 5.0 20.0	or

	Formulation	% w/w	
	Copolymer	75.0	or
	Stearyl alcohol	10.0	
	Mannitol	7.5	
	Sodium starch glycollate	7.5	
	Copolymer	80.0	or
	Stearyl alcohol	5.0	
	Pregelatinized Starch	10.0	
	Lactose monohydrate	5.0	
	Copolymer	80.0	or
	Stearyl alcohol	5.0	
	Sodium starch glycollate	10.0	
	Lactose monohydrate	5.0	
	Copolymer	75.0	or
	Stearyl alcohol	10.0	
	Sodium starch glycollate	10.0	
	Lactose monohydrate	5.0	
	Copolymer	85.0	or
	Stearyl alcohol	5.0	
	Sodium chloride	5.0	
	Lactose monohydrate	5.0	
	Copolymer	85.0	or
	Stearyl alcohol	5.0	
	Hydroxypropyl cellulose	5.0	
	Lactose monohydrate	5.0	
	Copolymer	85.0	or
	Stearyl alcohol	5.0	
	Hydroxypropylmethyl cellulose	5.0	
	Lactose monohydrate	5.0	
	Copolymer	80.0	or
	Stearyl alcohol	10.0	
	Hydroxypropylmethyl cellulose	5.0	
	Lactose monohydrate	5.0	

	Formulation	% w/w	
	Copolymer	80.0	or
	Stearyl alcohol	10.0	
	Sodium starch glycollate	5.0	
	Lactose monohydrate	5.0	
	Copolymer	80.0	or
	Stearyl alcohol	10.0	
	Hypromellose phthallate	5.0	
	Lactose monohydrate	5.0	
	Copolymer	80.0	or
	Stearyl alcohol	10.0	
	Low molecular weight hydroxypropyl cellulose	5.0	
	Lactose monohydrate	5.0	
	Copolymer	73.0	or
	Stearyl alcohol	12.0	
	Hydroxypropylmethyl cellulose	10.0	
	Lactose monohydrate	5.0	
	Copolymer	79.0	or
	Sodium dodecyl sulphate	1.0	
	Croscarmellose sodium	10	
	Sodium starch glycollate	10	
	Copolymer	80.0	or
	Croscarmellose sodium	10	
	Sodium starch glycollate	10	
	Copolymer	69.0	.
	Sodium dodecyl sulphate	1.0	
	Croscarmellose sodium	15	
	Sodium starch glycollate	15	

32. (Previously presented) The capsule shell composition according to Claim 1 which is:

Components	# (1) % w/w or	(2) w/w or	(3) w/w or	(4) w/w or	(5) w/w or	(6) w/w
Copolymer	45%	35%	25%	75%	65%	55%
Stearyl Alcohol	10%	10%	10%	10%	10%	10%
Lactose	5%	5%	5%	5%	5%	5%
Hydroxypropyl Cellulose	40%	50%	60%	10%	20%	30%
Total	100%	100%	100%	100%	100%	100%.

33. (Previously presented) The capsule shell composition according to Claim 1 which is:

Components	# (1) % w/w or	(2) w/w or	(3) w/w or	(4) w/w or	(5) w/w or	(6) w/w
Copolymer	63%	62.9%	62.75%	52%	42%	62%
Croscarmellose sodium	10%	10%	10%	15%	20%	5%
Sodium starch glycollate	10%	10%	10%	15%	20%	5%
Stearyl alcohol	12%	12%	12%	12%	12%	12%
Hydroxypropyl-methylcellulose	5%	5%	5%	5%	5%	15%
Sodium Dodecyl Sulphate	0%	0.1%	0.25%	1%	1%	1% .

34. (Cancelled)

35. (Previously presented) The capsule shell composition according to Claim 1 which is:

#	Formulation	%w/w	
1	Copolymer Hydroxypropylmethyl cellulose Lactose (regular) Glyceryl monostearate	73.0 10.0 5.0 12.0	or
2	Copolymer Hydroxypropylmethyl cellulose Lactose (regular) Hydroxypropylmethyl cellulose phthallate Stearyl alcohol	53.0 10.0 5.0 20.0 12.0	or
3	Copolymer Hydroxypropylmethyl cellulose Lactose (regular) Sodium dodecyl sulphate Stearyl alcohol	68.0 10.0 5.0 5.0 12.0	or
4	Copolymer Hydroxypropylmethyl cellulose Lactose (regular) Sodium dodecyl sulphate Stearyl alcohol	72.0 10.0 5.0 1.0 12.0	or
5	Copolymer Hydroxypropylmethyl cellulose Lactose (regular) Sodium dodecyl sulphate Stearyl alcohol	71.0 10.0 5.0 2.0 12.0	or

#	Formulation	%w/w	
6	Copolymer Sodium starch glycollate Lactose (regular) Sodium dodecyl sulphate Stearyl alcohol	62.0 20.0 5.0 1.0 12.0	or
7	Copolymer Sodium starch glycollate Lactose (regular) Stearyl alcohol	75.0 10.0 10.0 5.0	or
8	Copolymer Sodium starch glycollate Lactose (regular) Sodium dodecyl sulphate Stearyl alcohol	72.0 10.0 5.0 1.0 12.0	or
9	Copolymer Croscarmellose sodium Lactose (regular) Sodium dodecyl sulphate Stearyl alcohol	62.0 20.0 5.0 1.0 12.0	or
10	Copolymer Sodium starch glycollate Hydroxypropylmethyl cellulose Sodium dodecyl sulphate Stearyl alcohol	62.0 20.0 5.0 1.0 12.0	or

#	Formulation	%w/w	
11	Copolymer Hydroxypropylmethyl cellulose phthallate Hydroxypropylmethyl cellulose Sodium dodecyl sulphate Stearyl alcohol	62.0 20.0 5.0 1.0 12.0	or
12	Copolymer Sodium starch glycollate Hydroxypropylmethyl cellulose Sodium dodecyl sulphate Stearyl alcohol	62.5 20.0 5.0 0.5 12.0	or
13	Copolymer Croscarmellose sodium Sodium starch glycollate Hydroxypropylmethyl cellulose Sodium dodecyl sulphate Stearyl alcohol	62.0 10.0 10.0 5.0 1.0 12.0	or
14	Copolymer Croscarmellose sodium Hydroxypropylmethyl cellulose Sodium dodecyl sulphate Stearyl alcohol	67.0 15.0 5.0 1.0 12.0	or
15	Copolymer Croscarmellose sodium Hydroxypropylmethyl cellulose Sodium dodecyl sulphate Stearyl alcohol	72.0 10.0 5.0 1.0 12.0	or
16	Copolymer Croscarmellose sodium Hydroxypropylmethyl cellulose Sodium dodecyl sulphate Stearyl alcohol	77.0 5.0 5.0 1.0 12.0	or

#	Formulation	%w/w	
17	Copolymer	52.0	or
	Croscarmellose sodium	15.0	
	Sodium starch glycollate	15.0	
	Hydroxypropylmethyl cellulose	5.0	
	Sodium dodecyl sulphate	1.0	
	Stearyl alcohol	12.0	
18	Copolymer	42.0	or
	Croscarmellose sodium	20.0	
	Sodium starch glycollate	20.0	
	Hydroxypropylmethyl cellulose	5.0	
	Sodium dodecyl sulphate	1.0	
	Stearyl alcohol	12.0	
19	Copolymer	42.0	or
	Croscarmellose sodium	20.0	
	Sodium starch glycollate	20.0	
	Hydroxypropylmethyl cellulose	5.0	
	Sodium dodecyl sulphate	1.0	
	Stearyl alcohol	12.0	
20	Copolymer	62.0	or
	Croscarmellose sodium	5.0	
	Sodium starch glycollate	5.0	
	Hydroxypropylmethyl cellulose	15.0	
	Sodium dodecyl sulphate	1.0	
	Stearyl alcohol	12.0	
21	Copolymer	62.9	
	Croscarmellose sodium	10.0	
	Sodium starch glycollate	10.0	
	Hydroxypropylmethyl cellulose	5.0	
	Sodium dodecyl sulphate	0.1	
	Stearyl alcohol	12.0	.

36. (Cancelled)

37. (Cancelled)

38. (Previously presented) The capsule shell composition according to Claim 1 wherein the lubricant is stearyl alcohol present in an amount of 10 to 15% w/w, the surfactant is SDS or a block copolymer of ethylene oxide and propylene oxide present in an amount less than 5% w/w; and the dissolution modifying excipient is selected from a combination of HPC, HPMC, sodium starch glycollate, croscarmellose sodium, copovidone, xylitol or lactose.

39. (Previously presented) A capsule shell composition according to Claim 1 that is in the form of an injection molded capsule shell.

40. (Previously presented) A capsule shell composition according to Claim 1 that is in the form of a multicomponent injection molded capsule shell.

41 to 70 (cancelled).

71. (Previously presented) The capsule shell composition according to Claim 1 which is:

	Dissolution Modifier	Lubricant	Surfactant	
1	Hydroxypropylmethylcellulose (5%w/w)	Stearyl alcohol (12% w/w)	None	or
2	Hydroxypropylmethylcellulose (10%w/w), and HPMCphthalate (20%w/w)	Stearyl alcohol (12% w/w)	None	or
3	Hydroxypropylmethylcellulose (10%), and Lactose (5%)	Stearyl alcohol (12%)	None	or
4	Hydroxypropylmethylcellulose (5%)	Stearyl alcohol (12%)	SDS (1%) or Sodium Starch Glycollate (20%) or Tween or a polyoxypropylene-polyoxyethylene block copolymer .	

72. (Previously Presented) The capsule shell composition according to Claim 1 which is

#	Formulation	% w/w	
1	Copolymer	77.0	or
	Sodium Dodecyl Sulphate	1.0	
	Croscarmellose sodium	5.0	
	Stearyl Alcohol	12.0	
	Hydroxypropylmethyl Cellulose	5.0	
2	Copolymer	68.0	or
	Croscarmellose sodium	15.0	
	Stearyl Alcohol	12.0	
	Hydroxypropylmethyl Cellulose	5.0	
3	Copolymer	62.0	or
	Sodium Dodecyl Sulphate	1.0	
	Croscarmellose sodium	10.0	
	Sodium Starch Glycollate	10.0	
	Stearyl Alcohol	12.0	
	Hydroxypropylmethyl Cellulose	5.0	
4	Copolymer	63.0	or
	Croscarmellose sodium	10.0	
	Sodium Starch Glycollate	10.0	
	Stearyl Alcohol	12.0	
	Hydroxypropylmethyl Cellulose	5.0	
5	Copolymer	52.0	or
	Sodium Dodecyl Sulphate	1.0	
	Croscarmellose sodium	15.0	
	Sodium Starch Glycollate	15.0	
	Stearyl Alcohol	12.0	
	Hydroxypropylmethyl Cellulose	5.0	
6	Copolymer	62.0	or
	Polyoxypropylene-polyoxyethylene block copolymer	1.0	
	Sodium Starch Glycollate	20.0	
	Stearyl Alcohol	12.0	
	Hydroxypropylmethyl Cellulose	5.0	

#	Formulation	% w/w	
7	Copolymer polyoxypropylene-polyoxyethylene block copolymer Sodium Starch Glycollate Stearyl Alcohol Hydroxypropylmethyl Cellulose	62.0 1.0 20.0 12.0 5.0	or
8	Copolymer Stearyl Alcohol Croscarmellose sodium Sodium Starch Glycollate Hydroxypropylmethyl Cellulose Sodium Dodecyl Sulphate	62.0 12.0 5.0 5.0 15.0 1.0	or
9	Copolymer Stearyl Alcohol Croscarmellose sodium Sodium Starch Glycollate Hydroxypropylmethyl Cellulose Sodium Dodecyl Sulphate	42.0 12.0 20.0 20.0 5.0 1.0	or
10	Copolymer Stearyl Alcohol Sodium Starch Glycollate Hydroxypropylmethyl Cellulose Sodium Dodecyl Sulphate	47.0 12.0 10.0 30.0 1.0 .	

73. (Currently amended) A solid generally cylindrical linker body having an outer surface, the outer surface being exposed to a gastro-intestinal environment, the cylindrical linker body being composed of an extruded linker and injection molded composition comprising:

a copolymer of methyl acrylate, methyl methacrylate and methacrylic acid with a molar ratio of monomer units represented as 7:3:1, and a ratio of free carboxyl groups to esters groups of 1:10, present in an amount of about 20 to 90% w/w;

a lubricant present in an amount of 10 to about 30% w/w;

a combination of dissolution modifying excipients present in an amount of about 2.5 to about 70% w/w and wherein each of the dissolution modifying agents is selected from the group consisting of a swellable solid present in the range of about 5% to about 70%w/w, a non-reducing sugar present in the range of about 2.5 to 15% w/w; a water soluble filler present in the range of about 5 to 20%, a wicking agent present in the range of 5-10%, and a disintegrant present in the range of about 10 to 40%;

and optionally a surfactant present in an amount of less than 5% w/w, a plasticizer present in an amount of 0 to 10% w/w and/or a processing agent present in an amount of 0 to about 10% w/w;

wherein the linker composition is substantially pH-independent.

74. (Previously presented) The linker composition according to Claim 73 wherein the copolymer is present in an amount of about 50 to 90% w/w.

75. (Previously presented) The linker composition according to Claim 73 wherein the surfactant is a block copolymer of ethylene oxide and propylene oxide, lecithin, sodium dioctyl sulfosuccinate, sodium dodecyl sulphate, Polyoxyl 40 hydrogenated castor oil, polyoxyethylene sorbitan fatty acid esters, the sorbitan fatty acid esters, polyethylene glycol, Vitamin E-TPGS® (d-alpha-tocopheryl polyethylene glycol 1000 succinate), sucrose fatty acid ester; and combinations and mixtures thereof.

76. (Previously presented) The linker composition according to Claim 75 wherein the surfactant is sodium dodecyl sulphate present in an amount of less than 2% w/w.

77. (Previously presented) The linker composition according to Claim 75 wherein the surfactant is sodium dodecyl sulphate or is a block copolymer of ethylene oxide and propylene oxide.

78. (Previously presented) The linker composition according to Claim 77 wherein the surfactant is sodium dodecyl sulphate present in an amount of less than 2% w/w.

79. (Previously presented) The linker composition according to Claim 73 wherein the surfactant is a block copolymer of ethylene oxide and propylene oxide.

80. (Previously presented) The linker composition according to Claim 79 wherein the surfactant is sodium dodecyl sulphate present in an amount of less than 2% w/w.

81. (Previously presented) The linker composition according to Claim 73 wherein the lubricant is stearyl alcohol, glycerol monostearate (GMS), talc, magnesium stearate, silicon dioxide, amorphous silicic acid, or fumed silica; and combinations or mixtures thereof.

82. (Previously presented) The linker composition according to Claim 81 wherein the lubricant is stearyl alcohol.

83. (Previously presented) The linker composition according to Claim 82 wherein the stearyl alcohol is present from about 10 to about 15% w/w.

84. (Previously presented) The linker composition according to Claim 73 wherein at least one dissolution modifying excipient is a swellable solid which is ethyl cellulose, cellulose acetate phthalate; hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate, or other hydroxyalkylcellulose derivative; and combinations or mixtures thereof.

85. (Previously presented) The linker composition according to Claim 84 wherein the swellable solid is present in an amount of about 10 to 50% w/w.

86. (Previously presented) The linker composition according to Claim 84 wherein at least one dissolution modifying excipient is hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate, or hydroxypropyl cellulose; and combinations or mixtures thereof.

87. (Previously presented) The linker composition according to Claim 86 wherein the swellable solid is present in an amount of 10 to 50% w/w.

88. (Previously presented) The linker composition according to Claim 73 wherein at least one dissolution modifying excipient is selected from xylitol, mannitol, lactose, pregelatinized starch, sodium chloride, sodium starch glycollate, croscarmellose sodium, crospovidone (cross-linked polyvinyl pyrrolidone), copovidone, polyvinyl pyrrolidone; and combinations or mixtures thereof.

89. (Previously presented) The linker composition according to Claim 88 wherein the at least one dissolution modifying excipient is present in an amount of about 40 to 70% w/w.

90. (Previously presented) The linker composition according to Claim 89 wherein the at least one dissolution modifying excipient is a swellable solid and at least one other dissolution modifying excipient is selected from lactose, sodium starch glycollate, croscarmellose sodium, copovidone, crospovidone (cross-linked polyvinyl pyrrolidone), or polyvinyl pyrrolidone.

91. (Previously presented) The linker composition according to Claim 90 wherein at least one dissolution modifying excipient is hydroxypropylcellulose and at least one other dissolution modifying excipient is lactose.

92. (Previously presented) The linker composition according Claim 73 wherein at least one dissolution modifying excipient is a swellable solid and at least one other dissolution modifying excipient is selected from lactose, sodium starch glycollate, croscarmellose sodium, copovidone, crospovidone (cross-linked polyvinyl pyrrolidone), or polyvinyl pyrrolidone.

93. (Previously presented) The linker composition according to Claim 73 wherein the processing agent is talc.

94. (Previously presented) The linker composition according to Claim 93 wherein the processing agent is present in an amount of about 1 to about 5 % w/w.

95. (Previously presented) The linker composition according to Claim 91 wherein the processing agent is talc and is present in an amount of about 1 to about 5 % w/w.

96. (Previously presented) The linker composition according to Claim 73 which further comprises an absorption enhancer.

97. (Previously presented) The linker composition according to Claim 96 wherein the absorption enhancer is chitosan, lecithin, lectin, a sucrose fatty acid ester, Vitamin E-TPGS; and combinations or mixtures thereof.

98 to 111 (Cancelled)

112. (Previously presented) The capsule shell composition according to Claim 1 wherein the capsule shell has a wall thickness in the range of about 0.3 – 0.8 mm.

113. (Previously presented) The capsule shell composition according to Claim 1 wherein the capsule shell has a wall thickness in the range of about 0.3 mm to 0.5 mm.

114. (Previously presented) The capsule shell composition according to Claim 19 wherein the swellable solid is selected from ethyl cellulose, cellulose acetate phthalate; hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate, or other hydroxyalkylcellulose derivative, and combinations or a mixtures thereof.

115. (Previously presented) The capsule shell composition according Claim 1 wherein at least one dissolution modifying excipient is a distintegrant and at least one other dissolution modifying excipient is a non-reducing sugar.

116. (Previously presented) The capsule shell composition according Claim 115 wherein the disintegrant is sodium starch glycollate or croscarmellose sodium and the non-reducing sugar is xylitol, or mannitol.

117. (Previously presented) The capsule shell composition according to Claim 116 wherein the lubricant is stearyl alcohol.

118. (Previously presented) The capsule shell composition according Claim 1 wherein at least one dissolution modifying excipient is a distintegrant and at least one other dissolution modifying excipient is a water soluble filler.

119. (Previously presented) The capsule shell composition according Claim 118 wherein the disintegrant is sodium starch glycollate or croscarmellose sodium and the water soluble filler is lactose.

120. (Previously presented) The capsule shell composition according to Claim 119 wherein the lubricant is stearyl alcohol.

121. (Previously presented) The linker composition according to Claim 73 wherein the swellable solid is selected from ethyl cellulose, cellulose acetate phthalate; hydroxypropyl

cellulose, hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate, or other hydroxyalkylcellulose derivative, and combinations or a mixtures thereof.

122. (Previously presented) The linker composition according Claim 73 wherein at least one dissolution modifying excipient is a distintegrant and at least one other dissolution modifying excipient is a non-reducing sugar.

123. (Previously presented) The linker composition according Claim 122 wherein the disintegrant is sodium starch glycollate or croscarmellose sodium and the non-reducing sugar is xylitol, or mannitol.

124. (Previously presented) The linker composition according to Claim 123 wherein the lubricant is stearyl alcohol.

125. (Previously presented) The linker composition according Claim 73 wherein at least one dissolution modifying excipient is a distintegrant and at least one other dissolution modifying excipient is a water soluble filler.

126. (Previously presented) The linker composition according Claim 125 wherein the disintegrant is sodium starch glycollate or croscarmellose sodium and the water soluble filler is lactose.

127. (Previously presented) The linker composition according to Claim 126 wherein the lubricant is stearyl alcohol.

128. (Previously presented) The linker composition according to Claim 73 wherein the copolymer is present in an amount of about 50 to 90% w/w, the lubricant is stearyl alcohol present in an amount of about 10 to about 15% w/w, and at least one dissolution modifying excipient is hydroxypropylmethylcellulose, hydroxypropylcellulose, or a hydroxylalkyl cellulose derivative or salt thereof.

129. (Previously presented) The linker composition according to Claim 128 wherein the dissolution modifying excipient is lactose.

130. (Previously presented) The linker composition according to Claim 128 wherein at least one other dissolution modifying excipient is a disintegrant.

131. (Previously presented) The linker composition according to Claim 130 wherein the disintegrant is sodium starch glycollate, croscarmellose sodium, copovidone, crospovidone (cross-linked polyvinyl pyrrolidone), or polyvinyl pyrrolidone, or a combination or mixture thereof.

132. (Previously presented) The capsule shell composition according to Claim 25 wherein the at least one dissolution modifying excipient is lactose.

133. (Cancelled)

134. (Previously presented) The capsule shell composition according to Claim 26 wherein the disintegrant is sodium starch glycollate, croscarmellose sodium, copovidone, crospovidone (cross-linked polyvinyl pyrrolidone), or polyvinyl pyrrolidone, or a combination or mixture thereof.

135. (New) The capsule shell composition according to Claim 11 wherein the at least one dissolution modifying excipient is hydroxypropylcellulose.

136. (New) The capsule shell composition according to Claim 25 wherein the at least one dissolution modifying excipient is hydroxypropylcellulose.

REMARKS

Claims 1 to 33, 35, 38 to 40, and 71 to 97, 112 to 132 and 134-136 are pending in the application. Claims 135-136 have been added. Claims 1, 11, 14, 16, 25 and 73 have been amended. Support for amendments can be found throughout the specification, i.e., in claims as originally filed; in the working examples, or on pages 28, lines 4-18, page 34, lines 29-35 and page 35, lines 28-37 of the specification. No new matter is believed added.

Rejection of Claims under 35 USC §112

I. Rejection of Claims 1-33, 35, 38-40, 71-97 and 112-134 under 35 USC §112, first paragraph

Claims 1-33, 35, 38-40, 71-97 and 112-134 are rejected under 35 USC §112, first paragraph, as failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

The Examiner has rejected the claims listed above with respect to the limitation "wherein the extruded capsule shell composition is substantially independent". (See Office Action, page 2, 3rd ¶, last line).

Applicants respectfully point out that support for the aforementioned limitation can be found on Page 24, lines 33-36 and page 25 lines 1-2:

> "One aspect of the present invention is the novel blending of components which has the ability to render the poly(meth)acrylates, such as 4135F, which are pH dependent independent of this characteristic. ***They are no longer governed by the pH of the solution, i.e. the gastric tract, but are time/controlled release dependent instead,*** which determination is based upon the addition of the swellable solids and surfactants which will be described in further detail herein."[emphasis added].

The above paragraph clearly states that the polymer blend is no longer pH dependent, e.g. it is pH independent, and controlled by the time it takes to have excipients in the formulation, such as the above noted 'swellable solids' hydrate accordingly.

Therefore, Applicants have met the written description requirement accordingly with respect to inclusion of this term in the claims.

The Examiner further comments that:

> "Contrary to the limitation in the claims, the examples from the present specification show that the release of active agent from the capsule is indeed pH-dependent. See for example pages 45 and 48 for the dissolution rate at pH greater than 6 or 7.5. (See Office Action, page 2, 3rd ¶, last line, one page 3, 1rst ¶, first line).

Applicants respectfully maintain that the present specification indicates that release of active agent from a capsule of the present invention is pH independent for the reasons discussed below.

The specification teaches it is possible to have differing release rates of the contents of the capsule shell, and differing rates of release of the linker from the capsule subunits. These differing release rates are determined by polymeric composition that the capsule shells and subunits are composed of. The primary polymer along with the amounts of and types of excipients added to the polymer determine whether the release will be immediate or delayed. These releases are categorized in the specification on page 34 as "Fast Release/Pulse Capsules or Components", and on page 35 as "Slow/delayed Release/Pulse Capsules or Components".

Taking excerpts from the specification on page 34, lines 25-35, the "Fast Release/Pulse Capsules or Components" can be manipulated for production of an early release/pulse capsule or component in a multidosage capsule to have a 2-4 hour window. This is achieved by blending the Eudragit 4135F with the appropriate excipients, and extruding and injection molding the composition into thin walled component shells. In one preferred embodiment of the invention, the experimental section demonstrates that a formulation comprising the polymer 4135F with a surfactant and a swellable solid produces stable, injection molded components which can be reliably reproduced and injected from the mold with reduced, or no warpage of the shell.

In another embodiment of the invention, components made by blending 4135F with a swellable solid (hydroxypropylcellulose), at various percentages ranging from 10 to 70% were tested for their variance in a dissolution times, in an appropriate dissolution apparatus. Formulations containing 40 to 70 % Klucel were found to have similar dissolutions times (<2hours) in both simulated gastric fluid (SGF) and simulated intestinal fluids (SIF).

Dissolutions times for formulations containing 10 to 30% Klucel were found to be longer and more variable, although it is clear that this resulted in moldable components.

With respect to the "Slow/delayed Release/Pulse Capsules or Components", the specification on page 35, lines 1-14 teaches that:

> "the principal problem with Eudragit® 4135F in its unformulated state is its high dissolution time, in ***excess of 30 hours in aqueous media*** e.g. in SIF (simulated intestinal fluid). Therefore, to improve its dissolution time the polymer is blended with one or more hydrophilic excipients. This will enhance the absorption of water by the Eudragit 4135F polymer, and so accelerate the rate at which the blended polymer swells on absorption of water. As noted by the Experimental section herein, a ***dissolution modifying excipient, preferably a swellable solid excipient*** and optionally a second dissolution modifying excipient, such as a disintegrant, a lubricating agent, and if desired a surfactant, will produce a stable, injection molded component which can be reliably reproduced and injected from the mold with reduced, or no warpage of the shell." [emphasis added]

As noted, unformulated Eudragit® 4135F has a very high dissolution time, in excess of 30 hours in aqueous media e.g. in SIF (simulated intestinal fluid). SIF is the testing fluid used in the various USP apparatus's and is referenced in the specification on page 45 by the Examiner. SIF has a pH of about 7.5. SIF mimics the intestinal fluids.

The development of 4135F with the swellable solid hydroxypropylcellulose was intended to deliver pulsatile units with earlier release times than the combination of 4135F with the swellable solid HPMC in combination with lactose or the 4135F polymer combination with a super-disintegrant. Dissolution profiles which show that this was achieved with the inclusion of hydroxypropylcellulose (Klucel LF) is shown below in Figure 1. This data is referenced in the specification and cited above as "Formulations containing 40 to 70 % Klucel were found to have similar dissolutions times (<2hours) in both simulated gastric fluid (SGF) and simulated intestinal fluids (SIF)."

The profile in this Figure demonstrates that shells composed of a combination of 4135F and Klucel LF had a much reduced dissolution time, (over unformulated 4135F) which is *unaffected by media pH.*

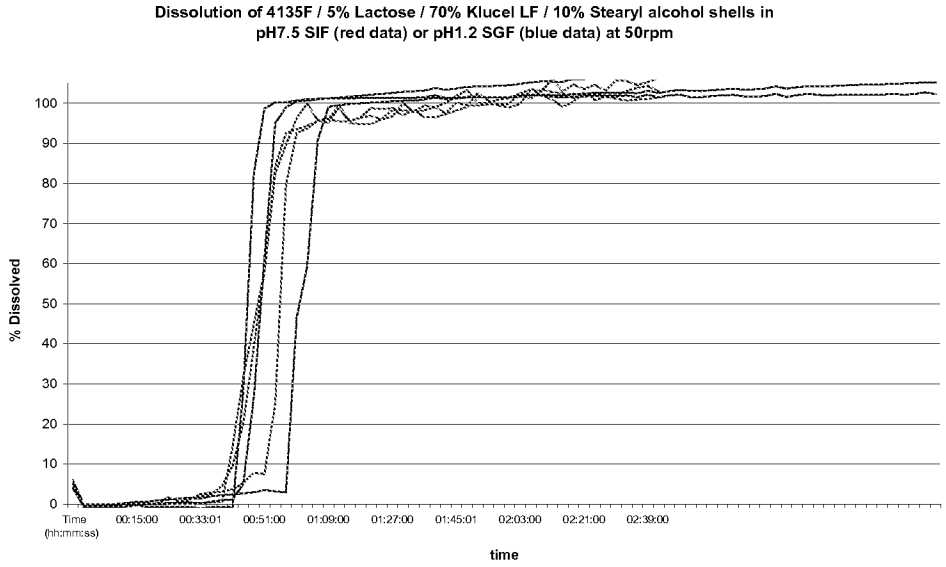


Figure 1: USP2 dissolution profile of 4135F/Klucel LF shells in SIF and SGF

This can be determined by looking at the blue lines which shows the dissolution of shells in pH 1.2 (e.g. Simulated Gastric Fluid) and those in the red lines which shows the dissolution of shells at pH 7.5 (e.g. Simulated Intestinal Fluid). As can be seen the red and blue lines overlap and appear quite similar. Thus, dissolution of these polymeric compositions is independent of the pH of the system in which they are tested in.

This clearly demonstrates that it is not only possible to manufacture shells with pulsatile release profiles, but that the release profiles are independent of buffer pH. The unmodified 4135F polymer therefore requires formulation modifications to achieve dissolution profiles which are comparable to other conventional enteric dosage forms.

Thus it is believed that Applicants have fully met the written description requirement, and that the specification fully supports this. Withdrawal of the rejection of these claims under 35 USC §112, first paragraph, is respectfully requested.

II. Rejection of Claim 25 under 35 USC §112, second paragraph

The Examiner has rejected claim 25 for the recitation of the phrase" at least one dissolution modifying excipient" in line 3. The Examiner points out that Claim 1 does not recite this

limitation, but instead requires "at least two dissolution modifying excipients" in the use of the phrase "combination".

Claim 25 has been amended to recite:

> "The capsule shell composition according to Claim 1 wherein the copolymer is present in an amount of about 50 to 90% w/w, the lubricant is stearyl alcohol present in an amount of about 10 to about 15% w/w, and the combination of dissolution modifying excipients contains at least one dissolution modifying excipient which is hydroxypropylmethylcellulose, hydroxypropylcellulose, or a hydroxylalkyl cellulose derivative or salt thereof. "

In view of this amendment and remarks, withdrawal of the rejection to claim 25 under 35 USC §112, second paragraph is respectfully requested.

Applicants have also amended claim 1 and 73 to recite "and a ratio of free carboxyl groups to esters groups of 1:10" with respect to the copolymer as in:

> "a copolymer of methyl acrylate, methyl methacrylate and methacrylic acid with a molar ratio of monomer units represented as 7:3:1, and a ratio of free carboxyl groups to esters groups of 1:10, present in an amount of about 20 to 90% w/w;

which is specifically disclosed in the manufactures data/specification sheet for the Eudragit 4135F. Applicants attach the specification sheet for the Examiner's convenience.

Rejection of Claims under 35 USC §103

The claims herein have three rejections as noted below:

I. Claims 1, 2 7-16, 20-22, 39, 40, 73, 74, 81-84, 87-90, 92-95, 112 and 113 are rejected under 35 USC §103(a) as being unpatentable over Petereit (US Pub. No. 2002/0160042), in view of Lehman et al, US 5,705,189 ('189).

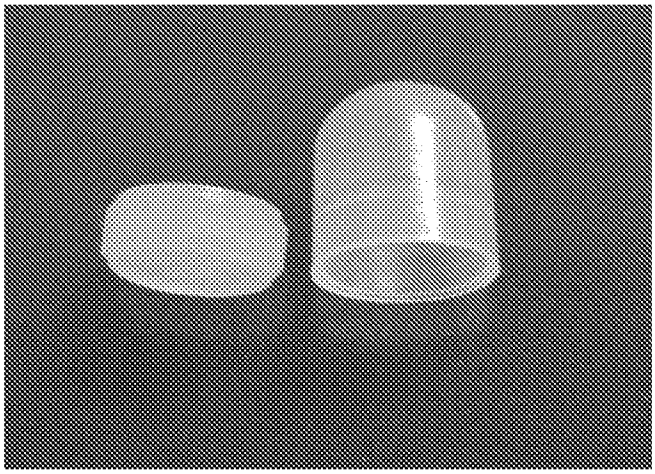
II. Rejection of Claims 3-6, 18 and 75-80 under 35 USC §103(a) over Petereit in view of Bolles (US 3,779,942) and Zentner (US 4,795,644).

III. Rejection of Claims 1-33, 35, 38-40, 71-97, 112-132 and 134 under 35 USC §103(a) over Petereit, in view of Lehmann I, Hatano (US 6,309,666) and Klug et al. (US 3,314809).

Applicants respectfully traverse all of these rejections. Although each of these rejections will be discussed independently below, the comments to Petereit is the primary reference will be referenced rather than repeated.

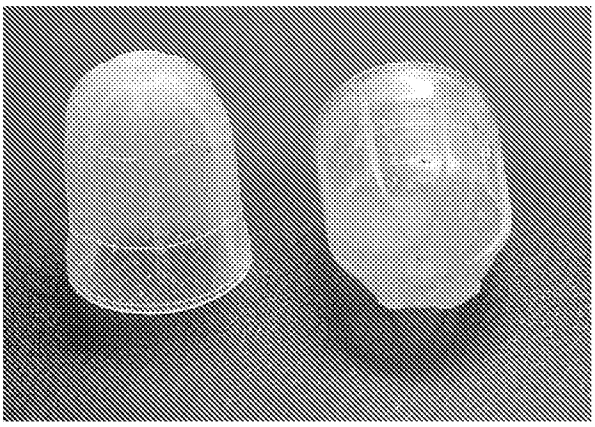
It should be noted that the Lehman Patent, US 5,705,189 ('189) has been referred to in earlier Office Actions and Responses as Lehman I, the details of which are incorporated by reference herein. The Petereit publication has also republished as US 2008/260814 (both of which correspond to previously cited WO 01/42935).

The present invention of independent claim 1 (capsule shells) and claim 73 (linkers) are directed to individual components of a multi-component dosage form. These components can include a capsule shell (of various sizes and shapes) and linker subunits, or end caps for shells, composed of these particular compositions. While representative pictures of capsules and sublinkers are disclosed in the Figures of the specification to assist the Examiner two of these pictures are produced below:



In the above Figure the linker subunit can easily be seen to have suitable ridges for the capsule component to be adhered or fixed to in a number of different ways.

In the Figure below an alternative capsule shape with ridges is demonstrated.



As noted in the specification the capsule shell and linker may be composed of the same or different compositions. Regardless of the composition of the subcomponents, they are meant to break apart at a particular time, and release the contents of the shell and/or linker to the GI tract at that time, all at once, not over a period of time as would be provided for in a controlled or constant rate of release. One dosage form that has a controlled, and constant rate of release of and active agent is the cited Zentner device, over which some of the claims are rejected herein.

The most frequently utilized capsule for drug delivery is a gelatin capsule. They are inexpensive, readily available, and provide what is termed 'immediate release'. When a gelatin capsule is administered, the capsule starts to immediately dissolve in the stomach and allows the contents of the capsule to be released into the gastrointestinal tract all at once (hence the term immediate release). In contrast, the 4135F polymeric blend of the instant invention instead provides for a capsule shell that has a more delayed, or prolonged time period before it releases the capsule contents into the GI tract. If a more immediate release of the capsule contents is desired, then a shell formulation which uses different polymers than the one claimed herein would be used. Such a capsule shell is described in copending application USSN 10/060,603 or USSN 10/470,439 which have claims directed to the polymer Eudragit E100, for instance.

Thus, when a multicomponent dosage form is assembled it is possible to have a shell subunit that disperses the contents as an immediate release, and be linked with a shell subunit that disperses the contents as a pulsitile release, much later down the GI tract. The same active or a different active can be filled into the capsule shells as desired.

A benefit of this invention is that the active agent need not be admixed with all the necessary excipients generally used for tableting. The greater the number of excipients the greater the chance for drug-excipient interactions which can affect stability of the active not just in shelf life, but with avoidance of potential degradants, etc. from these interactions.

The rejection under 35 USC §103(a) with respect to Petereit has been maintained, where the Examiner stats that Petereit:

> "…teaches injection-molded compositions comprising a) 45-100% methacrylate copolymers; b) 0.1-3% lubricant; c) 0-50% drier; d 0-30 plasticizer; e) 0-100% additives or auxiliaries; f) active agent; and g) 0-20% of another polymer of copolymer (paragraphs 0019-0027)." (See Office Action, page 3, 5th ¶); and
>
> Petereit "does not explicitly teach the claimed percent amount of lubricant from 5% to about 30%. However, difference in concentration will not support the patentability of subject matter encompassed by the prior art unless that is evidence indicating such concentration is critical…… In the present case, it would have been obvious to one of ordinary skill in the art to, by routine experimentation select a lubricant amount that falls within the claimed range with the expectation of at least similar result. This is because Petereit teaches the use of the same lubricant, such as stearyl alcohol, for the same purpose, namely, as a mold releasing agent (paragraphs 0041-0044). Further the use of lubricant as a mold releasing agent in the claimed amount is known in the art. See for example the teaching of Lehmann at column 3, lines 65-67; and example 1. Lehmann teaches the use of 6% of the mold releasing agent, based on the weight of the polymer. Accordingly, it would have been obvious to one of ordinary skill in the art to modify the molding compositions of Petereit using lubricant in the claimed amount in view of the teaching of Lehmann." (See Office Action, page 4, 2nd ¶).

Applicants respectfully traverse the above-identified rejection for these reasons.

Petereit et al. teaches an improvement in an injection molding process that includes a devolatilization step. The purpose of this devolatilization step is for removing residual traces of water from the copolymer which would interfere with the injection molding of the final product.

The formulation of the copolymer blend used in the Petereit process does not teach a combination of two (2) dissolution modifying agents as required by claim 1 herein. One of the dissolution modifying excipients for use in the instant invention is a swellable solid. In Petereit, there is no express statement of swellable solids, but use of a second copolymer. The copolymer is an optional excipient in Petereit's blend, being present from 0-20% w/w. Consequently, the resulting blend does NOT require such an excipient to being present.

The list of polymers suitable for use in the Petereit formulation in disclosed in paragraph 0080 shown below. This paragraph provides for a long list of many polymers not claimed or disclosed for use within the context of Applicants invention as a dissolution modifying excipient. Therefore, even if a copolymer is present one would not necessarily be directed to pick and choose as an excipient that one which Applicant describes as a dissolution modifying excipient.

Further, Paragraph 0080 does not provide for combinations or mixtures of these polymers as required by Applicants.

More importantly, and which has been raised previously, paragraph 0080 contains an error. As can be readily seen the recitation of hydroxypropylcellulose is followed by the abbreviation of HPMC as "hydroxypropylcellulose (HPMC)". However, HPMC stands for hydroxypropyl**methyl** cellulose NOT hydroxypropylcellulose. Therefore it is unclear if Petereit meant to include HPC or meant to include HPMC in the list of polymers disclosed therein.

> **[0080]** Examples of these other polymers are: polyvinylpyrrolidones, polyvinyl alcohols, cationic (meth)acrylate copolymers made from methyl methacrylate and/or ethyl acrylate and 2-dimethylaminoethyl methacrylate (EUDRAGIT® E100), carboxymethylcellulose salts, hydroxypropylcellulose (HPMC), neutral (meth)acrylate copolymers made from methyl methacrylate and ethyl acrylate (dry matter from EUDRAGIT® NE 30 D), copolymers made from methyl methacrylate and butyl methacrylate (PLASTOID® B) or (meth)acrylate copolymers with quaternary ammonium groups and containing trimethylammonioethyl methacrylate chloride as monomer (EUDRAGIT® RL and/or EUDRAGIT® RS).

Consequently, all of the limitations of Applicant's Claim 1 are not present in the Petereit '042 publication.

The Lehman I '189 patent is directed to compositions which are pH dependent and dissolve in the intestinal juices, for use as controlled release coating agents. (see Abstract) In column 2, lines 31-36, Lehman states:

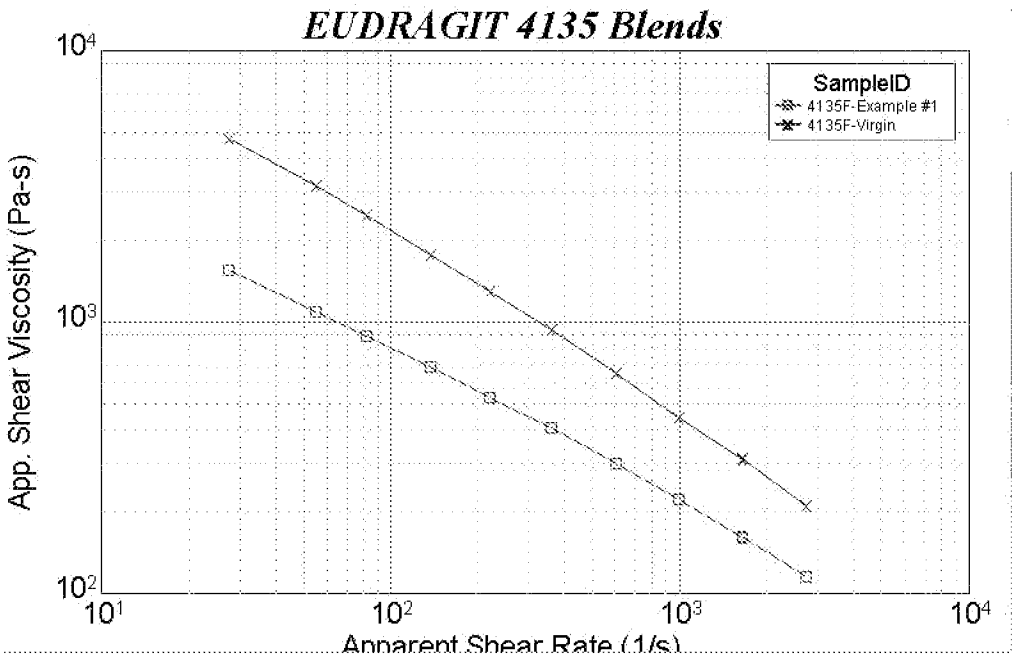
> "Drug coating produced therefrom,….. are not soluble in gastric juice at a pH 1 to 2 and in intestinal juices or buffer solutions with pH values $\leq$5, but can dissolve well in intestinal juices at pH values of 5.5 to 8."

This teaches formulations which are pH dependent, not pH independent. The presently amended claims, are however, directed to capsule shells and linkers molded from a composition which is **substantially pH independent.**

The Lehman I copolymer materials while primarily oriented towards drug coatings (Column 1, lines 61 to 67; and Column 2, lines 1 to 8) are generally described as being thermoplastic when comprised of 16-40% acrylic and/or methacrylic acid, and 30-80% methyl acrylate, and which may also contain alkyl esters of acrylic and/or methacrylic acid (see, column 2, lines 54-61, and claim 1).

The copolymers of the '189 patent are anionic polymers. The compositions described in the '189 patent have characteristics which make them thermoplastic, and require particular conditions and excipients as defined therein in order to be molded, see Column 2, lines 20 to 36. However, this description and the claims of the Lehman I patent do **not** describe the polymeric component used herein, known as Eudragit 4135F. This particular copolymer is described in Column 6, as emulsion polymer E2. The E2 polymer contains 10% methacrylic acid, **not** the 16-40% w/w which is stated as being within the compositions having thermoplastic moldable characteristics. In Lehman, the E2 copolymer is also **not** admixed with the additional agents as stated on Column 3, lines 62 to 67, and Column 4, lines 1 and 2 therein.

Applicants specification, page 24, lines 1 to 3 states that the polymers described in the '189 patent have increased viscosity's relative to the blended compositions as used herein. There is no motivation, or teachings in the Lehman I patent to change the viscosity of the compositions in the manner as claimed herein to achieve Applicants invention. Viscosity changes are necessary in order to readily extrude and injection mold the components. See Figure 15 of the instant application (reproduced below) which compares the virgin 4135F polymer with a representative composition of the instant invention, Example 1.



The Examiner states that Petereit teaches use of the:

> "same lubricant, such as stearyl alcohol, for the same purpose namely as a mold releasing agent (paragraphs 0041-0044). Further, the use of lubricant as a mold releaseing agent in the claimed amount is known in the art. See for example the teaching of Lehmann at column 3, lines 65-67l and example 1. Lehmann teaches the use 6% of the mold releasing agent, based on the weight of the polymer" (see page 4, Office Action).

Lehmann teaches use of a mold-release agent which is disclosed as glycerol monostearate and di-stearate, mixtures of these two and stearic acid, and metal salts thereof. Lehmann does not teach nor suggest use of stearyl alcohol. Example 1 of Lehmann does disclose 6% by wt of glycerol monostearate.

Petereit discloses 0.1 to 3% by wt of a release agent in paragraph 0041:

> [0041] The mixture comprises from 0.1 to 3% by weight, preferably from 0.2 to 1% by weight, of a release agent, based on the (meth)acrylate copolymer.

Petereit discloses Paragraph 0043-44 describe suitable mold release agents:

[0043] Examples of release agents (mould-release agents) are:

[0044] esters of fatty acids or fatty amides, aliphatic long-chain carboxylic acids, fatty alcohols and esters of these, montan waxes, paraffin waxes, and metal soaps, and particular mention should be made of glycerol monostearate, stearyl alcohol, glycerol behenate, cetyl alcohol, palmitic acid, carnauba wax, beeswax, etc.

The Examiner states that "it would have been obvious to one of ordinary skill in the art to modify the molding composition of Petereit using lubricant in the claimed amount in view of the teaching of Lehmann".

Applicant's claim 1 has a "lubricant present in an amount of 5 to about 30% w/w". Claim 7, dependent upon claim 1 has "the lubricant is present in an amount of about 10 to 25 % w/w". Claim 9 is directed to stearyl alcohol, and claim 10 is wherein "the stearyl alcohol is present from about 10 to about 15% w/w".

The Examiner's argument does not make sense however. Lehman discloses glycerol monostearate. Petereit includes glycerol monostearate in their list of mold-release agents. In fact, Example 2 of Petereit uses glycerol monostearate. Petereit is an improvement by the same manufacturer as Lehmann. Petereit specifically choose to reduce the amount of mold release agent needed in the formulation used in the process therein. There would be no motivation to direct the skilled artisan to then increase the amount of mold release agent in the Petereit formulation. There is no suggestion or teaching in Petereit or Lehmann to use 10-25% w/w of a mold release agent (as required in claim 7). There is no teaching or suggestion to specifically use stearyl alcohol in amounts of about 10 to about 15% w/w as required by claim 9.

Consequently all of the limitations of Claim 1, and those dependent thereon that are not present in the '042 publication are not achieved by the teachings of Lehman I patent.

The mere fact that references can be combined or modified is not sufficient to establish *prima facie* obviousness. MPEP § 2143.01 at 2100-131. There must be something in the prior art to suggest the desirability of the combination. *Id.; see also, In re Mills,* 916 F.2d 680, 16 U.S.P.Q. 2d 1430 (Fed. Cir. 1990).

There is nothing in Lehman I to explain the incorporation of particular substituents, such as a combination of two dissolution modifying excipients (Claim 1) or a combination of a swellable solid and lactose, or super disintegrant (Claim 16), or a combination of two dissolution modifying excipients and a surfactant (Claim 1 and 18), etc., with similar claims for the linker subunit.

Indeed, the Lehman et al. reference would teach the skilled artisan that Applicants additional excipients and additives are not needed as their thermoplastic compositions are deemed suitable for molding based solely upon the addition of glycerol monostearate as a mold release agent. This would suggest that the skilled person that would not be motivated to make any substitution or additions whatsoever to the compositions of Lehman. The skilled artisan

This also does not address the inclusion of a combination of dissolution modifying excipients, the specific w/w% amounts of these excipients and of the lubricants and surfactants as claimed by Applicants. As noted above, the Examiner has also not provided any basis for an article of manufacture which is the linker subunit. Although the linker composition is the same as that of the capsule shell wall, it is a linker subunit which is being claimed having that composition, not the composition itself. No cited references teach or describe this unit, having these particular characteristics

It should be noted that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention **where there is some teaching, suggestion or motivation to do so** found either in the references or in the knowledge generally available to one of ordinary skill in the art. The test for obviousness is not whether the features of the secondary references may be bodily incorporated into the structure of the primary reference; nor is it that the claimed invention must be expressly suggested in any one or all of the references. Rather, the test is **what the combined teachings** of the references would have suggested to those of ordinary skill in the art.

Even with the combined teachings of the references discussed above, nothing therein would teach, suggest or motivate one of ordinary skill in the art to combine these teachings to obtain the presently claimed molded capsule shell or dosage unit compositions.

Therefore, the USPTO has failed to establish a *prima facie* case of obviousness for the claims as presented herein.

II. Rejection of Claims 3-6, 18 and 75-80 under 35 USC §103(a) over Petereit in view of Bolles (US 3,779,942) and Zentner (US 4,795,644)

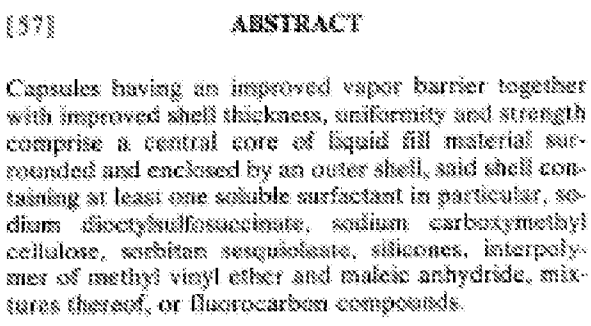
Claims 3-6, 18 and 75-80 are rejected under 35 USC §103(a) as being unpatentable over Petereit (US Pub. No. 2002/0160042) in view of Bolles (US 3,779,942, herein after '942) and Zentner (US 4,795,644, herein after '644). Applicants respectfully traverse this rejection.

For all the reasons described previously in the first §103(a) rejection which is incorporated herein there is no teaching, suggestion, motivation or reason provided in Petereit for making capsule shell and linker compositions that are substantially pH independent, and have the required limitations as shown in Claim 1 herein.

The Examiner cites the '942 Bolles reference for teaching a capsule shell composition comprising well known polymers such as:

> "hydroxypropylcellulose, and a surfactant such as sodium dioctyl sulfosuccinate in an amount of from about 0.001-10% (abstract; and column 2, lines 20-59)". (See Office Action, page 5, 4th ¶).

There is no mention of HPC in the abstract. The abstract (shown below), discusses a liquid fill material surrounded and enclosed by an outer shell, the outer shell containing at least one soluble surfactant (which can be SDS).



[57] ABSTRACT

Capsules having an improved vapor barrier together with improved shell thickness, uniformity and strength comprise a central core of liquid fill material surrounded and enclosed by an outer shell, said shell containing at least one soluble surfactant in particular, sodium dioctylsulfosuccinate, sodium carboxymethyl cellulose, sorbitan sesquioleate, silicones, interpolymer of methyl vinyl ether and maleic anhydride, mixtures thereof, or fluorocarbon compounds.

Column 2 of the '942 patent discusses compatible surfactants for use in the soft fill capsule. The polymer hydroxypropylcellulose is mentioned on column 1, lines 67 onto column 2,

lines 1-2. Example 18 of the '942 patent appears to use hydroxypropylmethylcellulose and Example 20 appears to use hydroxypropylcellulose C to make the soft capsule shell.

The '942 patent references US patent 3,423,489 ('489) as the apparatus and method for the encapsulation technology used in the improvement disclosed therein. The process of the '489 patent produces not an extruded and injection molded subunit as required by the claims herein, but a liquid filled encapsulated soft capsule capsule.

The temperature and pressures needed to extrude and injection mold the shells and linker subunits herein is not the same as that of the encapsulation process. The general process used in the '489 patent is shown below, taken from Column 2, lines 18-61:

This invention makes possible the formation of capsules by physical means at extremely high production rates, in the order of 36,000 to 130,000 capsules per orifice per minute, and by virtue of its ability to encapsulate aqueous liquids makes possible for the first time the economically practical encapsulation of water soluble chemical components for subsequent use in chemically reactive systems. The invention further makes possible the production of well-formed capsules having excellent sphericity, uniform wall thicknesses, and leakproofness. In some embodiments, unlike previously known processes, the process is independent of the surface tensions of the liquids, i.e., it is possible to encapsulate low surface tension liquids within high surface tension liquids.

Briefly summarized, the present invention involves forming a concentric biliquid column having an inner core of liquid to be encapsulated and an outer tube of hardenable liquid encapsulating material which is caused to travel as a stream in a trajectory path for a time sufficient to allow the column to constrict due to natural forces, i.e. cohesive forces, surface tension and the like, first into a "string of capsules" and then ultimately into individual droplets or capsules in which the encapsulating material completely encloses the encapsulated liquid. The encapsulating material is congealed sufficiently upon separation of the stream into individual capsules to withstand impact upon falling. If desired the process conditions can be controlled to produce connected strings of capsules by congealing the encapsulating material sufficiently to maintain the connecting strands intact, thus preventing separation of the stream into individual capsules. It is much preferred to direct the biliquid column or stream to travel through a gaseous medium, such as air in a state or free fall in a trajectory path having horizontal components, rather than into a liquid medium.

A preferred method of forming a biliquid column is by forcing a jet of fill liquid through a body of liquid encapsulating material, the jet being directed to cause the resulting biliquid column to follow the desired trajectory. The column is apparently formed by frictional forces between the fast moving jet of fill liquid and the encapsulating liquid which enables the fill liquid stream to drag along with it a concentric shell of the encapsulating liquid, which shell is rapidly accelerated to a velocity equal to that of the fill liquid as due to momentum exchange

The soft liquid fill capsule obtained by the process of the '489 and the addition of the surfactants in the '942 patent do not teach nor suggest a pH independent copolymer blend of methyl acrylate, methyl methacrylate and methacrylic acid polymers which are pH independent, and release the contents of their rigid capsule shell within particular parameters.

In contrast to the '942 soft capsule, the shell of the claimed invention is required to have a wall thickness in the range of about 0.3 – 0.8 mm (Claim 112). It is unclear how the Examiner would achieve this limitation using the technology of the '942 patent. Additionally, the article claimed herein is a subunit. The subunits are meant to be assembled together to a multi-compartment unit, including a shell and a linker and optionally additional shells. The '942 patent does not produce a 'subunit'. It does not produce a unit which can be filled with other than a liquid.

As distinguished from the claimed invention, the '942 patent produces a completed unit dosage form, whereas the instant claims merely produce shells and subunits which can be filled and clipped/welded with other filled subunits having differing actives. The '942 will only be liquid filled with one active. The '942 capsule is not directed towards having multiple subunits with differing release rates. The'942 capsule is not going to be able to achieve multiple subunits with differing release rates and different actives (if desired).

The Bolles reference would not teach or direct the skilled artisan to add a polymer such as 4135F to the encapsulation formulation, nor be motivated to alter the Petereit thermoplastic compositions suitable for molding and achieve the molded articles as claimed herein. The additional excipients and additives which are missing from the Petereit reference, are not satisfied by the teachings of Bolles.

Bolles also does not address the inclusion of a combination of dissolution modifying excipients, the specific w/w% amounts of these excipients and of the lubricants and surfactants as claimed by Applicants. It solely addresses surfactants within a completely different system.

The Zentner reference is cited by the Examiner for is inclusion of a particular surfactant (see Office Action, page 5 last line). The Zentner device is directed to a rather complex drug delivery device which uses charged insoluble resins bearing electrostatic charges identical to that of the intended drug to be used in the device. The drug needs to be a water-soluble diffusible ionized drug. There is no such requirement for this in the instant invention.

Zentner delivers a drug as a controlled rate of release. The goal of Zentner is to deliver to the GI tract a drug at a substantially constant rate, regardless of the pH of the GI tract (See column 2, lines 63-69). The device is also meant to maintain its physical and chemical integrity throughout the release period (column 3, lines 12-14). This is clearly not what the instant invention is intended to do.

In the present invention:

1) the capsule shell and/or linker is meant to break apart at a particular time, and release the contents of the shell/linker to the GI tract at that time, all at once, not over a period of time to provide a controlled constant rate of release;

2) the 4135F polymeric formulations provide for a capsule shell that has a more delayed, or prolonged time period to release the capsule contents into the GI tract; than a gelatin capsule which is of the immediate release;

3) when a multicomponent dosage form of the present invention, is assembled it is possible to have a shell subunit that disperses the contents as an immediate release, and be linked to a second, or third, etc. shell subunit that disperses the contents as pulsitile releases, much later down the GI tract; and

4) prior to the disclosure by Applicants it was not believed possible to prepare a pH-independent **capsule shell or linker itself** using the copolymers as recited in the presently amended claims.

Neither the Petereit reference alone or taken with Bolles or Zentner teaches the skilled artisan how to achieve these individual components, alone or as a multicompartment dosage form having the characteristics as described herein.

The reasons for inclusions of lubricants or surfactants within the Bolles or Zentner disclosure does not provide any meaning for inclusion within the instant formulation. Neither of these references have the same issues or problems encountered by Applicants in their development. Neither Bolles nor Zentner teach extruded and injection molded components.

Simply because Zentner includes a surfactant into the disclosed device does not direct the skilled artisan to look at this device and extrapolate it use therein for a completely different activity.

There is no teaching, suggestion, motivation or reason for one of ordinary skill in the art to use the teachings of Petereit alone or with Bolles and Zentner to result in the substantially pH independent composition and articles of manufacture as claimed in the present invention. Bolles and Zentner do not make up for the deficiencies of Petereit with respect to changing the pH dependency of the compositions described in those references, and in fact further exemplifies the unexpectedness of the presently claimed invention.

Therefore, the claimed invention is not prima facie obvious, and withdrawal of the rejection of these claims under 35 USC §103(a) is respectfully requested.

III. Rejection of Claims 1-33, 35, 38-40, 71-97, 112-132 and 134 under 35 USC §103(a) over Petereit, in view of Lehmann I, Hatano (US 6,309,666) and Klug et al. (US 3,314809).

Claims 1-33, 35, 38-40, 71-97, 112-132 and 134 are rejected as being unpatentable under 35 USC §103(a) over Petereit (US2002/0160042), in view of Lehmann (US 5,705,189, also referred to therein as Lehman I), Hatano (US 6,309,666) and Klug et al. (US 3,314809, hereinafter '809). Applicants respectfully traverse this rejection.

As Petereit, and Lehman I are discussed supra, please see the above comments. Hatano has also previously been discussed in Applicants prior responses which are incorporated by reference herein.

In summary, Hatano does not disclose a molding process for making capsule shell/linker components, nor the molded articles which are capsule shell and/or linker components. Hatano is interested in providing a modified dosage form which uses pre-existing capsule shells and coats these shells to provide for particular release features.

The Hatano et al. patent discloses a pulse release dosage form having the following characteristics:

1. An enteric layer (acrylic copolymer) that dissolves when the unit enters the small intestine and is exposed to pH>5.5;
2. An inner layer of the Eudragit E100 polymer that swells and hydrates, but does not dissolve;

3. Fluid enters the capsule body (dissolving the gelatin or HPMC capsule shell wall) at a rate determined by the thickness of the E100 coating and begins to dissolve the acidic capsule contents, and
4. Dissolution of the E100 layer is controlled by the amount and/or type of acid contained within the capsule fill, and the thickness of the E100 coating.

The film-coating usage disclosed in Hatano this form a multi-layer construct of film coats on top of a capsule shell wall, wherein the hard capsule shell has both an enteric coating and an inner layer coating applied on top of the capsule shell wall. It is the combination of coatings on the shell that provide for the delayed release characteristics of the final dosage form as shown in Hatano. The film-coating composition controls the release of the contents of the capsule shell which it surrounds. In contrast it is the composition of the shell itself (when injection molded into the capsule shell) when combined with other capsule shells and/or linker subunits of the same or differing compositions that control the release of the release of the contents of the capsule shell. A skilled artisan would not look to the Hatano to achieve a formulation that is pH independent, nor a formulation that can be extruded and injection molded into an article of manufacture.

Klug '809 patent appears to be cited by the Examiner for a teaching of a capsule shell that comprises HPC. (See Office Action, page 7, 2nd ¶). The Klug patent describes a process for making thermoplastic articles with an HPC polymer. The HPC used in the Klug process is the primary polymer and requires a particular degree of substitution, etc. for use therein. While Klug provides for additional excipients which can be added, they are limited to "anti-oxidants, fillers, pigment and the like" without any specific embodiments being listed. (See Column 5, lines 12-16).

As noted supra, Petereit provides for incorporation of another polymer into the blend (see paragraph 0080) but does not provide for combinations of these polymers in the blend. Petereit is also unclear as to whether HPMC or HPC was meant to be included in the long list of suitable and additional polymers which might be added to the formulation.

As noted, Klug is cited by the Examiner to teach that the skilled artisan would be motivated to select HPC as the "other" polymer to be added to the capsule shell composition of Petereit. Given the ambiguity displayed in Petereit this is an improper conclusion and is improperly using hindsight rejection in view of Applicants disclosure. However, even if this

were true, why would the skilled artisan necessarily pick and choose a swellable solid which is HPC or HPMC from the long list of polymers cited in Petereit?

More specifically, Petereit taken with any of these references does not teach a combination of excipients as required in Claim 1. Lehman I does not teach nor suggest all the limitations present in claim 1. The secondary references of Hatano do not provide the missing excipients, nor does Klug.

Consequently, none of the references alone or in combination, provides any teaching, suggestion, or motivation to one of ordinary skill in the art to combine these references to and obtain a pH independent capsule shell or linker subunit having the claimed composition herein. Therefore, reconsideration, and withdrawal of the rejection of these claims under 35 USC §103(a) is respectfully requested.

In response to Applicants prior arguments, the Examiner comments "that nowhere in the Petereit reference is there a teaching of pH-dependency disclosed". The argument appears to be made that Petereit teaches the use of the same copolymer and in the same amount. "Where the claimed and prior art products are identical or substantially identical in structure or composition, a prima facie case of either anticipation or obviousness has been established". (See Office Action, page 8, 1rst full ¶).

Applicants contest the Examiner's view that the Petereit reference teaches "identical or substantially identical in structure or composition" to that claimed herein. As has been pointed out above, the limitations of Claim 1 have not been achieved by Petereit alone or in combination with the various cited references. The naked or virgin polymer does not dissolve in a pH independent manner. The instant application provides clear data that the compositions, when tested as a capsule shell with drug. in a USP II or III apparatus in suitable media, such as SIF do not display pH dependency but are independent of pH in their release of the contents. This limitation in Claim 1 is not the only difference between Applicants and the rejections under 35 USC §103(a) herein.

The appropriate test is **what the combined teachings** of the references would have suggested to those of ordinary skill in the art. Even with the combined teachings of the references discussed above, nothing therein would teach, suggest or motivate one of

ordinary skill in the art to combine these teachings to obtain the presently claimed molded capsule shell or dosage unit compositions.

Therefore, the USPTO has failed to establish a *prima facie* case of obviousness for the claims as presented herein.

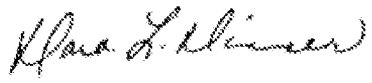
Applicants respectfully request withdrawal of each of the above identified rejections to the claims under 35 USC §103(a).

CONCLUSION

Reconsideration and withdrawal of the rejections based on 35 USC §112 and §103, and the prompt issuance of a Notice of Allowance, is respectfully requested. Should the Examiner have any questions or wish to discuss any aspect of this application, the Examiner is encouraged to call the undersigned attorney at the number below. If the Examiner does not find the claims allowable, Applicants respectfully request an interview with the Examiner at the earliest opportunity.

It is not believed that this paper should cause any additional fees or charges to be required, other than expressly provided for already. However, if this is not the case the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,



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Röhm Pharma Polymers

Preliminary specifications, test methods and processing characteristics for Präparat 4135 F (Preparation 4135 F)

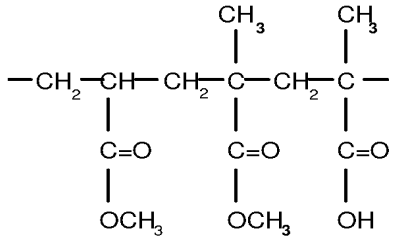
Preliminary specifications

1 Commercial form

Solid substance obtained from EUDRAGIT® FS 30 D by stress coagulation and extrusion, the product contains small amounts of Sodium Laurylsulfate Ph. Eur. / NF. and Polysorbate 80 Ph. Eur. / NF.

2 Chemical structure

Präparat 4135 F is a copolymer of methyl acrylate, methyl methacrylate and methacrylic acid.



The ratio of the free carboxyl groups to the ester groups is approx. 1:10.
The average molecular weight is approx. 220,000.

3 Characters

Description

Colourless to yellow tinged granules with a faint characteristic odour

Solubility

1 g of Präparat 4135 F dissolves in 7 g aqueous acetone (H_2O 3% w/w) to give a clear solution or in 7 g 1 N sodium hydroxide solution to give a slightly cloudy solution.
The solid substance is practically insoluble in petroleum ether.

4 Tests

Dry substance (DS)

Not less than 97 %.
According to Ph.Eur. “Loss on drying”, method d, approx. 1 g of the granules is dried for 3 hours at 110°C.

Assay

9.2 – 12.3 % methacrylic acid units on dry substance (DS)

Acid value: 60 - 80 mg KOH per g of dry substance

The assay is performed according to Ph. Eur. "Potentiometric titration" or USP <541>.
Approx. 2.0 g of Präparat 4135 F are dissolved in 90 ml isopropyl alcohol and 10 ml water.
Titration is performed with 0.5 N sodium hydroxide (NaOH).
A blank value is determined under the same conditions.
1 ml 0.5 N NaOH corresponds to 43.045 mg methacrylic acid units.

$$\text{Methacrylic acid units (\%) on DS} = \frac{\text{ml 0.5 N NaOH} \cdot 430.45}{\text{sample weight (g)} \cdot \text{DS (\%)}}$$

The acid value (AV) states how many mg KOH are required to neutralize the acid groups contained in 1 g dry substance.

$$\text{AV (mg KOH / g DS)} = \text{methacrylic acid units (\%)} \cdot 6.517$$

5 Purity

Sulphated ash / Residue on ignition

Max. 0.2 % according to Ph. Eur. 2.4.14 or USP <281>.
1 g Präparat 4135 F is used for the test

Heavy metals

Max. 20 ppm according to Ph. Eur. 2.4.8 method C or USP <231> method II.
1 g Präparat 4135 F is used for the test.

Monomers

Max. 500 ppm, determined by means of liquid chromatography according to Ph. Eur. 2.2.29 or USP <621>.

Sample solution:
Dissolve 1.00 g of Präparat 4135 F in acetone p.a. and dilute to 50.0 ml.
Add 10.0 ml of the solution drop wise to 40 ml of a 70 % solution of methanol for chromatography in water. Centrifuge for 5 min at 6000 rpm and use the supernatant solution as the test solution.

Reference solutions:
Pipette 10.0 mg of methyl acrylate to 5 ml of iso-butanol and dilute to 50.0 ml with acetone p.a. Dilute 1.0 ml of the solution to 100.0 ml with acetone p.a. Take 10.0 ml of this solution and mix with 40 ml of a 70% solution of methanol for chromatography in water. Pipette 10.0 mg of methacrylic acid and 10.0 mg of methyl methacrylate to 5 ml of iso-butanol and dilute to 50.0 ml with acetone p.a. Dilute 1.0 ml of the solution to 100.0 ml with acetone p.a. Take 10.0 ml of this solution and mix with 40 ml of a 70 % solution of methanol for chromatography in water.

Procedure: The chromatographic procedure may be carried out using:
- a column 120 mm long and 4.6 mm in internal diameter packed with octadecylsilyl silica gel for chromatography R (7 µm) Ph. Eur. (USP: L1),
- as mobile phase at a flow rate of 2 ml per minute a mixture of 20 volumes of methanol R and 80 volumes of phosphoric acid pH 3.8,
- as detector a spectrophotometer set at 200 nm.

Inject separately equal volumes (about 20 µl) of each solution.

Calculate the content of monomers from the height of the peaks in the chromatograms obtained with the sample solution and the reference solutions, from the content of monomers in the reference solutions and from the sample weight.

Microbial count
Max. 1,000 CFU / g; Salmonella not detectable in 10 g, E. coli, S. aureus, Ps. aeruginosa not detectable in 1 g. The test is performed according to Ph. Eur. 2.6.12 and 2.6.13.

6 Identity testing

Proof of identity is furnished by IR spectroscopy on a dry film of Präparat 4135 F approx. 15 µm thick.

To obtain the film, some drops of an approx.10 - 15 % solution of Präparat 4135 F in acetone is placed on a crystal disc of KBr and dried in vacuum for about 2 hours at 70 °C.

The location and intensity of the bands correspond to Figure 1.
The figure shows the characteristic band of the C = O vibrations of the esterified carboxyl groups at 1732 cm^{-1}, which overlaps the band of the C = O vibrations of the carboxylic acid groups at 1705 cm^{-1}. Further ester vibrations are detected at 1166, 1196, 1235 and 1263 cm^{-1}. The wide absorption range of associated OH Groups between 2500 and 3500 cm^{-1} is superimposed by CH_X vibrations at 2900 – 3000 cm^{-1}. Further CH_X vibrations can be discerned at 1386, 1439 and 1447 cm^{-1}.

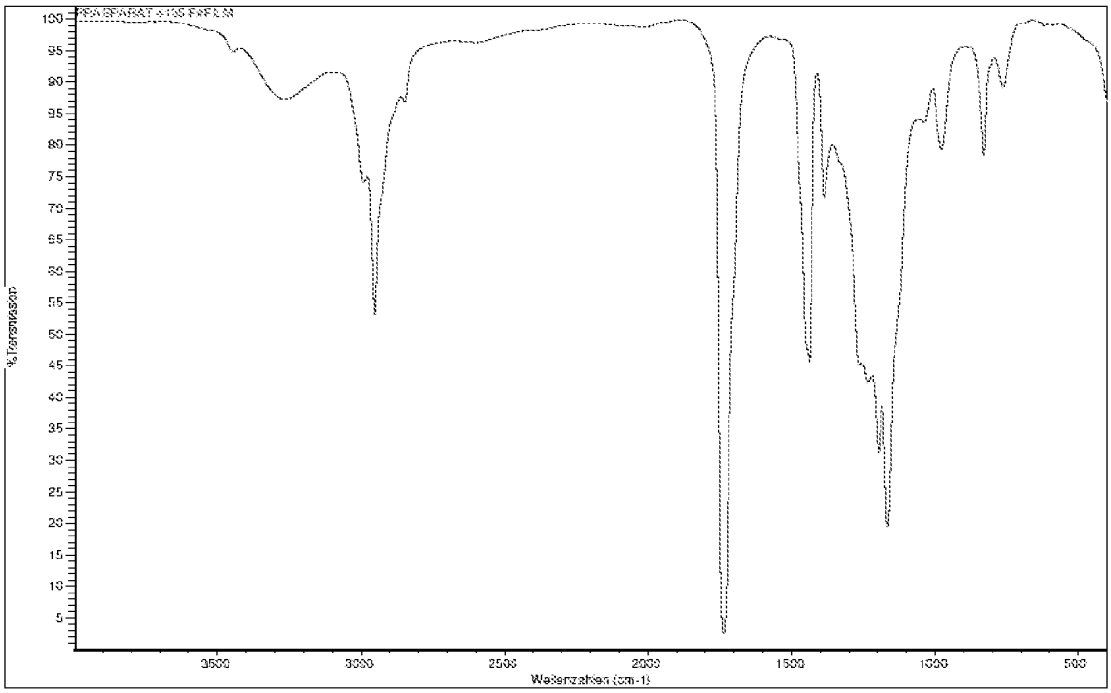


Figure 1: IR spectrum of Präparat 4135 F

7. Storage and handling:

Protect from warm temperature (USP, General Notices)
Protect from moisture.

8. Stability:

Storage stability data are available upon request.

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Attorney Docket No. P51223
Customer No.: 20462

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	McAllister et al.	7 August 2009
Serial No.:	10/470,438	Group Art Unit No.: 1618
Filed:	06 January 2004	Examiner: J. Rogers
For:	PHARMACEUTICAL FORMULATION	

Commissioner for Patents
P. O. Box 1450
Alexandria, VA 22313-1450

Amendment

Sir:

In response to the Examiner's Action mailed 9 February 2009, having a shortened statutory period of 3 months, please enter the following Remarks and Amendments into the record. Enclosed herewith is a petition for three (3) month extension of the shortened statutory period set by the Examiner and authorization to charge the required fee to the indicated deposit account.

Amendments to the Claims begin on page 2 of this paper.

Remarks begin on page 19 of this paper.

Amendments to the Claims

This listing of claims will replace all prior versions, and listings, of claims in the application:

Claims 1 to 41 (Cancelled).

42.(Currently amended) A multi-component pharmaceutical dosage form which comprises a plurality of sub-units, each sub-unit being selected from

a) a drug substance-containing capsule compartment which is soluble or disintegrable in a patient's gastro-intestinal environment for release of the drug substance contained in the capsule compartment; and

b) a solid generally cylindrical body having an outer surface, the outer surface being exposed to a gastro-intestinal environment, the cylindrical body being composed of an extruded an injection molded material comprising a pharmaceutical composition comprising:

a copolymer of methyl acrylate, methyl methacrylate and methacrylic acid, with molar ratio of monomer units of 7:3:1, and a ratio of free carboxyl groups to esters groups of 1:10, present in an amount of about 20 to 90% w/w,

at least one dissolution-modifying excipient selected from the group consisting of a swellable solid, disintegrant, non-reducing sugar, water soluble filler, wicking agent, and an inorganic salt present in an amount of about 2.5 to about 70% w/w,

a lubricant present in an amount of 10 to about 30% w/w,

and optionally a surfactant present in an amount of less than 5% w/w, a plasticizer present in an amount of 0 to 10% w/w, and/or a processing agent present in an amount of 0 to about 10% w/w,

wherein the pharmaceutical composition is substantially pH-independent ~~and is soluble, dispersible or disintegrable in a patient's acidic gastric environment and~~

~~neutral-to-basic intestinal environment~~,

and wherein the cylindrical body ~~is comprised of the extruded material and~~ is capable of time-controllably releasing the drug substance contained in the capsule compartment into the patient's gastro-intestinal environment,

and in which, at least prior to administration to a patient, the sub-units are assembled together into a dosage form.

43.(cancelled)

44.(Previously Presented) A multi-component pharmaceutical dosage form according to Claim 46, in which the lubricant is present in an amount from about 10 to about 15% w/w.

45.(Previously Presented) A multi-component pharmaceutical dosage form according to Claim 42, in which the surfactant is a block copolymer of ethylene oxide and propylene oxide, lecithin, sodium dioctyl sulfosuccinate, sodium dodecyl sulphate, Polyoxyl 40 hydrogenated castor oil, polyoxyethylene sorbitan fatty acid esters, the sorbitan fatty acid esters, polyethylene glycol, Vitamin E-TPGS® (d-alpha-tocopheryl polyethylene glycol 1000 succinate), sucrose fatty acid ester; or combinations and mixtures thereof.

46.(Previously Presented) A multi-component pharmaceutical dosage form according to Claim 42, in which the lubricant is stearyl alcohol.

47.(Previously Presented) A multi-component pharmaceutical dosage form according to Claim 42, wherein the at least one dissolution-modifying excipient is a disintegrant selected from the group consisting of sodium starch glycolate, croscarmellose sodium, copovidone, and crospovidone, and combinations or mixtures thereof, present in an amount of about 10 to about 40 % w/w.

48.(cancelled)

49.(Previously Presented) A multi-component pharmaceutical dosage form according to Claim 47, in which the lubricant is stearyl alcohol present in an amount from about 10 to about 15% w/w.

50.(Currently amended) A multi-component pharmaceutical dosage form according to Claim [[47]] 42 , in which the at least one dissolution modifying excipient is a swellable solid selected from the group consisting of ethyl cellulose, cellulose acetate phthalate; hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate, and other hydroxyalkylcellulose derivatives, and combinations or mixtures thereof, present in an amount of about 10 to 50% w/w.

51. (Currently amended) A multi-component pharmaceutical dosage form according to Claim [[47]] 42, in which the processing agent is talc present in an amount of about 1 to about 5% w/w.

52. (Currently amended) A multi-component pharmaceutical dosage form according to Claim [[47]] 42, in which at least one of the sub-units is a drug substance-containing capsule having a wall with a thickness in the range of about 0.3 – 0.8 mm.

53.(Previously Presented) A multi-component pharmaceutical dosage form according to Claim 42, in which at least one of the sub-units releases the drug substance into the patient's gastro-intestinal environment as a substantially immediate release.

54.(Previously Presented) A multi-component pharmaceutical dosage form according to Claim 42 which at least one of the sub-units releases the drug substance into the patient's gastro-intestinal environment as a sustained release or pulsed release.

55.(cancelled)

56.(Currently amended) A process for making a pharmaceutical dosage form comprising the steps of:

a) introducing

a copolymer of methyl acrylate, methyl methacrylate and methacrylic acid, with molar ratio of monomer units of 7:3:1, and a ratio of free carboxyl groups to esters groups of 1:10, and

an excipient composition comprising:

a lubricant present in an amount of about 10 to about 25% w/w;

at least one dissolution-modifying excipient selected from the group consisting of a swellable solid, disintegrant, non-reducing sugar, water soluble filler, wicking agent, and an inorganic salt present in an amount of about 2.5 to about 70% w/w[[,]] ; and

optionally a surfactant present in an amount of 0 to 10%, a plasticizer present in an amount of 0 to 10% w/w and/or a processing agent present in an amount of 0 to about 10% w/w;

simultaneously, and at substantially the same location, into an elongated hot melt extruder;

b) mixing said copolymer and said excipient composition in the hot melt extruder to form a homogeneous composition therein to render the homogeneous composition substantially pH-independent, and ejecting the homogeneous composition in the form of a strand from the hot melt extruder though a die at a location remote from said same location at which the copolymer and said excipient composition are introduced;

c) cutting the strand into pellets;

d) introducing said pellets into an injection molder and forming subunits of a thin-walled capsule compartments, or a solid generally cylindrical body ~~matrix~~ subunits from said pellets by injection molding.

57.(Previously Presented) The process according to Claim 56, in which the excipient composition comprises at least one dissolution modifying excipient which is a swellable solid selected from ethyl cellulose, cellulose acetate phthalate, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate, or other hydroxyalkylcellulose derivative; or combinations or mixtures thereof.

58.(Previously presented) The process according to Claim 56, in which the excipient composition comprises a surfactant which is sodium dodecyl sulphate or is a block copolymer of ethylene oxide and propylene oxide, present in an amount of less than 5% w/w.

59.(Previously Presented) The process according to Claim 56, in which the lubricant is selected from the group consisting of stearyl alcohol, glycerol monostearate (GMS), talc, magnesium stearate, silicon dioxide, amorphous silicic acid, and fumed silica; and combinations or mixtures thereof.

60.(original) The process according to Claim 56, in which the hot melt extruder is maintained at a temperature not exceeding approximately 135°C.

61.(Previously presented) The process according to Claim 56, in which the hot melt extruder is maintained at a temperature not lower than the copolymer and said excipient composition melting points.

62. (Previously presented) The process according to Claim 56, in which the temperature in the hot melt extruder gradually increases along the length of the hot melt extruder, from said same location at which the copolymer and an excipient composition are introduced, to the die, the maximum temperature not exceeding approximately 135°C.

63. (Previously presented) The process according to Claim 56, in which the hot melt extruder comprises an elongated barrel having first and second opposite ends, and twin screws within the barrel for propelling copolymer and said excipient composition along the length of the interior of the barrel, said substantially same location at which the copolymer and said excipient composition are introduced is located adjacent the first end of the barrel, and said die is located adjacent the second end of the barrel.

64. (original) The process according to Claim 56, in which the injection molding of the thin-walled capsule compartments is carried using an injection molder having a barrel and a

nozzle, while maintaining the injection molder barrel at a temperature in the range of about 120°C to 140°C.

65. (original) The process according to Claim 56, in which the injection molding of the thin-walled capsule compartments is carried using an injection molder having a barrel and a nozzle, while maintaining the injection molder nozzle at a temperature in the range of about 140°C to 190°C.

66. (original) The process according to Claim 56, in which the injection molding of the thin-walled capsule compartments is carried using an injection molder having a barrel and a nozzle, while maintaining the injection molder nozzle at a temperature of about 165 to 170°C.

67. (original) The process according to Claim 56, in which the injection molding of the thin-walled capsule compartments is carried using an injection molder having a barrel and a nozzle, while maintaining the injection molder barrel at a temperature in the range of about 120°C to 140°C and maintaining the injection molder nozzle at a temperature in the range of about 140°C to 190°C.

68. (original) The process according to Claim 56 wherein the pharmaceutical dosage forms are assembled using said capsule compartments as components of said dosage forms.

69. (original) The process according to Claim 68 wherein the said capsule compartments of the assembled dosage form are connected together by at least one weld where adjacent parts of said components are in contact.

70. (original) The process according to Claim 69 wherein the weld is produced by a thermal weld, an ultrasonic weld, an inductive weld, or an adhesive weld.

71. (Currently amended) A method of administering to a patient in need thereof, a multi-component pharmaceutical dosage form which comprises at least two subunits, each

sub-unit being selected from

a) a generally cylindrical body having an outer surface, the outer surface being exposed to a gastro-intestinal environment, the cylindrical body being composed of an extruded material comprising a pharmaceutical composition, the composition being soluble, dispersible or disintegrable in a patient's gastro-intestinal environment; and

b) a drug substance-containing capsule compartment comprising a shell having an outer surface and an opposed inner surface, the inner surface defining at least in part a confined space for holding a drug substance, and the outer surface being exposed to a gastro-intestinal environment, the shell being composed of an extruded an injection molded material comprising a pharmaceutical composition comprising:

a copolymer of methyl acrylate, methyl methacrylate and methacrylic acid, with molar ratio of monomer units of 7:3:1, and a ratio of free carboxyl groups to esters groups of 1:10, present in an amount of about 20 to 90% w/w,

at least one dissolution-modifying excipient selected from the group consisting of a swellable solid, disintegrant, non-reducing sugar, water soluble filler, wicking agent, and an inorganic salt present in an amount of about 2.5 to about 70% w/w,

a lubricant present in an amount of 10 to about 30% w/w,

and optionally a surfactant present in an amount of less than 5% w/w, a plasticizer present in an amount of 0 to 10% w/w, and/or a processing agent present in an amount of 0 to about 10% w/w,

wherein the pharmaceutical composition is substantially pH-independent and ~~instead~~ has a time-dependent sustained or controlled rate of release of a drug substance from the capsule component,

and wherein the shell material between and including the inner and outer surfaces is composed of the extruded and injection molded material; and

in which, at least prior to administration to a patient, at least two of the sub-units are assembled together into a dosage form.

72.(Currently amended) The method ~~A multi-component pharmaceutical dosage form~~ according to Claim 79 in which the composition of the shell comprises a lubricant which is stearyl alcohol, present in an amount from about from about 10 to about 15% w/w.

73.(Currently amended) The method ~~A multi-component pharmaceutical dosage form~~ according to Claim 71, in which the composition of the shell comprises a surfactant selected from a block copolymer of ethylene oxide and propylene oxide, lecithin, sodium dioctyl sulfosuccinate, sodium dodecyl sulphate, Polyoxyl 40 hydrogenated castor oil, polyoxyethylene sorbitan fatty acid ester, sorbitan fatty acid ester, polyethylene glycol, d-alpha-tocopheryl polyethylene glycol 1000 succinate, or a sucrose fatty acid ester, [[and]] or combinations and mixtures thereof.

74. (Currently amended) The method ~~A multi-component pharmaceutical dosage form~~ according to Claim 71 in which the composition of the shell comprises a processing agent which is talc present in an amount of about 1 to about 5% w/w.

75. (Currently amended) The method ~~A multi-component pharmaceutical dosage form~~ according to Claim 71 wherein the at least one dissolution modifying excipient is a swellable solid which is ethyl cellulose, cellulose acetate phthalate, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate, or other hydroxyalkylcellulose derivatives; or combinations or mixtures thereof.

76. (Currently amended) The method ~~A multi-component pharmaceutical dosage form~~ according to Claim 75 wherein the dissolution modifying excipient is selected from the group consisting of hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate, or hydroxypropyl cellulose, and combinations or mixtures thereof.

77. (Currently amended) The method ~~A multi-component pharmaceutical dosage form~~

according to Claim 75 wherein the swellable solid is present in an amount of about 10 to 50% w/w.

78.(Currently amended) The method ~~A multi-component pharmaceutical dosage form~~ according to Claim 73, wherein the surfactant is sodium dodecyl sulphate or a block copolymer of ethylene oxide and propylene oxide, present in an amount of less than 5% w/w.

79.(Currently amended) The method ~~A multi-component pharmaceutical dosage form~~ according to Claim 71, wherein the lubricant is stearyl alcohol, glycerol monostearate (GMS), talc, magnesium stearate, silicon dioxide, amorphous silicic acid, or fumed silica; or combinations or mixtures thereof.

80.(Currently amended) The method ~~A multi-component pharmaceutical dosage form~~ according to Claim 79, wherein the lubricant is stearyl alcohol present in an amount from about 10 to about 15% w/w ; and the at least one dissolution-modifying excipient is a disintegrant selected from sodium starch glycolate, croscarmellose sodium, copovidone, or crospovidone, and combinations or mixtures thereof; and a second dissolution modifying excipient which is a swellable solid selected from ethyl cellulose, cellulose acetate phthalate, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate, or other hydroxyalkylcellulose derivatives; or combinations or mixtures thereof.

81.(Currently amended) The method ~~A multi-component pharmaceutical dosage form~~ according to Claim 71 wherein the composition of the shell comprises a dissolution modifying excipient which is a combination of a swellable solid and lactose, sodium starch glycollate, croscarmellose sodium, copovidone, crospovidone (cross-linked polyvinyl pyrrolidone), or polyvinyl pyrrolidone.

82.(Currently amended) The method ~~A multi-component pharmaceutical dosage form~~ according to Claim 81 wherein the dissolution modifying excipient is hydroxypropylcellulose and lactose.

83. (Currently amended) The method ~~A multi-component pharmaceutical dosage form~~ according to Claim 71 wherein the composition of the shell comprises a dissolution modifying excipient which is xylitol, mannitol, lactose, pregelatinized starch sodium chloride, sodium starch glycollate, croscarmellose sodium, crospovidone (cross-linked polyvinyl pyrrolidone), copovidone, or polyvinyl pyrrolidone, or combinations or mixtures thereof.

84. (Currently amended) The method ~~A multi-component pharmaceutical dosage form~~ according to Claim 83 wherein the dissolution modifying excipient is present in an amount of about 40 to 70% w/w.

85. (Currently amended) The method ~~A multi-component pharmaceutical dosage form~~ according to Claim 71, wherein the copolymer in the composition of the shell is present in an amount of about 50 to 90% w/w, the dissolution modifying excipient is hydroxypropylmethylcellulose, hydroxypropylcellulose, or a hydroxylalkyl cellulose derivative or salt thereof, and the lubricant is stearyl alcohol.

86. (Currently amended) The method ~~A multi-component pharmaceutical dosage form~~ according to Claim 85, wherein the dissolution modifying excipient also includes a disintegrant.

87.(Currently amended) The method ~~A multi-component pharmaceutical dosage form~~ according to Claim 86, wherein the disintegrant is sodium starch glycollate, croscarmellose sodium, copovidone, crospovidone (cross-linked polyvinyl pyrrolidone), or polyvinyl pyrrolidone, or a combination or mixture thereof.

88.(Currently amended) The method ~~A multi-component pharmaceutical dosage form~~ according to Claim 42 wherein the dissolution modifying excipient is a swellable solid which is ethyl cellulose, cellulose acetate phthalate, hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate, or other hydroxyalkylcellulose derivative; or combinations or mixtures thereof.

89.(Currently amended) The method ~~A multi-component pharmaceutical dosage form~~ according to Claim 88 wherein the dissolution modifying excipient is hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate, or hydroxypropyl cellulose.

90.(Currently amended) The method ~~A multi-component pharmaceutical dosage form~~ according to Claim 89 wherein the swellable solid is present in an amount of about 10 to 50% w/w.

91.(Previously Presented) A multi-component pharmaceutical dosage form according to Claim 42 wherein the dissolution modifying excipient is a non-reducing sugar selected from xylitol or mannitol, present in the range of about 2.5 to 15% w/w; a water soluble filler which is lactose present in the range of about 5 to 20% w/w, or an inorganic salt which is sodium chloride present in the range of about 5-10% w/w , or combinations or mixtures thereof.

92. (Previously presented) A multi-component pharmaceutical dosage form according to Claim 42, wherein the copolymer is present in an amount of about 50 to 90% w/w, the dissolution modifying excipient is hydroxypropylmethylcellulose, hydroxypropylcellulose, or a hydroxylalkyl cellulose derivative or salt thereof, and the lubricant is stearyl alcohol.

93. (Previously presented) A multi-component pharmaceutical dosage form according to Claim 42 wherein the dissolution modifying excipient is a combination of a swellable solid and lactose, sodium starch glycollate, croscarmellose sodium, copovidone, crospovidone (cross-linked polyvinyl pyrrolidone), or polyvinyl pyrrolidone.

94.(Previously presented) A multi-component pharmaceutical dosage form according to Claim 93 wherein the dissolution modifying excipient is hydroxypropylcellulose and lactose.

95.(Cancelled)

96. (Currently amended) A multi-component pharmaceutical dosage form according to Claim [[95]] 42,wherein the lubricant is stearyl alcohol present from about 10 to about 15%

w/w.

97.(Previously Presented) A multi-component pharmaceutical dosage form according to Claim 42, wherein the polymeric composition comprises a surfactant which is a block copolymer of ethylene oxide and propylene oxide, lecithin, sodium dioctyl sulfosuccinate, sodium dodecyl sulphate, Polyoxyl 40 hydrogenated castor oil, polyoxyethylene sorbitan fatty acid esters, sorbitan fatty acid esters, polyethylene glycol, Vitamin E-TPGS® (d-alpha-tocopheryl polyethylene glycol 1000 succinate), sucrose fatty acid ester; or combinations and mixtures thereof.

98.(Previously presented) The process according to Claim 56, wherein the plasticizer is selected from the group consisting of triethyl citrate (TEC), tributyl citrate, acetyl triethyl citrate (ATEC), acetyl tributyl citrate (ATBC), dibutyl phthalate, dibutyl sebacate (DBS), diethyl phthalate, vinyl pyrrolidone glycol triacetate, polyethylene glycol, polyoxyethylene sorbitan monolaurate, propylene glycol, and castor oil; and combinations or mixtures thereof.

99.(Currently amended) A multi-component pharmaceutical dosage form according to Claim 42, wherein the copolymer is present in an amount of about 50 to 90% w/w, the dissolution modifying excipient is a swellable solid selected from hydroxypropylmethylcellulose, hydroxypropylcellulose, or a hydroxylalkyl cellulose derivative or salt thereof, and the lubricant is stearyl alcohol.

100.(Currently amended)) A multi-component pharmaceutical dosage form according to Claim 99, wherein the dissolution modifying excipient ~~also~~ includes a second dissolution modifying excipient which is a disintegrant.

101.(Previously Presented) A multi-component pharmaceutical dosage form according to Claim 100, wherein the disintegrant is sodium starch glycollate, croscarmellose sodium, copovidone, crospovidone (cross-linked polyvinyl pyrrolidone), or polyvinyl pyrrolidone, or a combination or mixture thereof, present in an amount about 10 to 40% w/w.

102.(Previously presented) The method ~~A multi-component pharmaceutical dosage form~~ according to Claim 71 in which the solid cylindrical body further comprises a drug substance.

103.(Previously presented) A multi-component pharmaceutical dosage form according to Claim 102 in which the drug substance is released into the patient's gastro-intestinal environment as a sustained release or pulsed release.

104.(Previously Presented) The method ~~A multi-component pharmaceutical dosage form~~ according to Claim 71 wherein the dissolution modifying excipient is a non-reducing sugar selected from xylitol or mannitol, present in the range of about 2.5 to 15% w/w; a water soluble filler which is lactose present in the range of about 5 to 20% w/w, or an inorganic salt which is sodium chloride present in the range of about 5-10% w/w or combinations or mixtures thereof.

105.(Previously Presented) A multi-component pharmaceutical dosage form according to Claim 101 wherein the disintegrant is present in an amount of about 20 to 30% w/w.

106.(New) The method according to Claim 71 wherein the drug substance containing capsule comprises a drug selected from the group consisting of analgesics, anti-inflammatory agents, anthelmintics, anti-arrhythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, antiepileptics, antihistamines, antihypertensive agents, antimuscarinic agents, antimycobactefial agents, antineoplastic agents, immunosuppressants, antithyroid agents, antiviral agents, anxiolytic sedatives, astringents, beta-adrenoceptor blocking agents, blood products and substitutes, cardiac inotropic agents, corticosteroids, cough suppressants, diagnostic agents, diuretics, dopaminergics, haemostatics, immunological agents, lipid regulating agents, muscle relaxants, parasympathomimetics, parathyroid calcitonin and biphosphonates, prostaglandins, radiopharmaceuticals, sex hormones, steroids, anti-allergic agents, stimulants, anorexics, sympathomimetics, thyroid agents, PDE IV inhibitors, NK3 inhibitors, CSBP/RK/p38 inhibitors, antipsychotics, vasodilators and xanthines.

107.(New) A multi-component pharmaceutical dosage form which comprises a plurality of sub-units, each sub-unit being selected from

a) a drug substance-containing capsule compartment which is soluble or disintegrable in a patient's gastro-intestinal environment for release of the drug substance contained in the capsule compartment; and

b) a solid generally cylindrical body having an outer surface, the outer surface being exposed to a gastro-intestinal environment, the cylindrical body being composed of an extruded an injection molded material comprising a pharmaceutical composition comprising:

a copolymer of methyl acrylate, methyl methacrylate and methacrylic acid, with molar ratio of monomer units of 7:3:1, and a ratio of free carboxyl groups to esters groups of 1:10, present in an amount of about 20 to 90% w/w,

at least one dissolution-modifying excipient selected from the group consisting of

i) a swellable solid selected from polyvinyl pyrrolidone, poly(ethylene)oxide, ethyl cellulose, cellulose acetate phthalate, hydroxypropylmethyl cellulose phthalate hydroxypropylcellulose, hydroxypropylmethyl cellulose present in the range of about 5% to about 70%w/w;

ii) a disintegrant selected from sodium starch glycolate, croscarmellose sodium NF, copovidone and crospovidone (cross-linked polyvinyl pyrrolidone), and combinations or mixtures thereof present in the range of about to 10 to 40%,

iii) a non-reducing sugar selected from xylitol or mannitol present in the range of about 2.5 to 15% w/w;

iv) a water soluble filler selected from lactose present in the range of about 5 to 20% w/w;

v) a wicking agent selected from mannitol, lactose, and starch present in an amount of about 2.5 to about 70% w/w; and

vi) an inorganic salt which is sodium chloride present in the range of about 5 to 10% w/w;

a lubricant selected from the group consisting of stearyl alcohol, glycerol monostearate (GMS), talc, magnesium stearate, silicon dioxide, amorphous silicic acid, or fumed silica; and combinations or mixtures thereof present in an amount of

10 to about 30% w/w,

and optionally a surfactant present in an amount of less than 5% w/w, a plasticizer present in an amount of 0 to 10% w/w, and/or a processing agent present in an amount of 0 to about 10% w/w,

wherein the pharmaceutical composition is substantially pH-independent and wherein the cylindrical body is capable of time-controllably releasing the drug substance contained in the capsule compartment into the patient's gastro-intestinal environment,

and in which, at least prior to administration to a patient, the sub-units are assembled together into a dosage form.

108.(New) A method of administering to a patient in need thereof, a multi-component pharmaceutical dosage form which comprises at least two subunits, each sub-unit being selected from

a) a generally cylindrical body having an outer surface, the outer surface being exposed to a gastro-intestinal environment, the cylindrical body being composed of an extruded material comprising a pharmaceutical composition, the composition being soluble, dispersible or disintegrable in a patient's gastro-intestinal environment; and

b) a drug substance-containing capsule compartment comprising a shell having an outer surface and an opposed inner surface, the inner surface defining at least in part a confined space for holding a drug substance, and the outer surface being exposed to a gastro-intestinal environment, the shell being composed of an extruded an injection molded material comprising a pharmaceutical composition comprising:

a copolymer of methyl acrylate, methyl methacrylate and methacrylic acid, with molar ratio of monomer units of 7:3:1, and a ratio of free carboxyl groups to esters groups of 1:10, present in an amount of about 20 to 90% w/w,

at least two dissolution-modifying excipients selected from the group consisting of a swellable solid, disintegrant, non-reducing sugar, water soluble filler, wicking agent,

and an inorganic salt, present in an amount of about 2.5 to about 70% w/w,

a lubricant present in an amount of 10 to about 30% w/w,

and optionally a surfactant present in an amount of less than 5% w/w, a plasticizer present in an amount of 0 to 10% w/w, and/or a processing agent present in an amount of 0 to about 10% w/w,

wherein the pharmaceutical composition is substantially pH-independent and has a time-dependent sustained or controlled rate of release of a drug substance from the capsule component,

and wherein the shell material between and including the inner and outer surfaces is composed of the extruded an injection molded material; and

in which, at least prior to administration to a patient, at least two of the sub-units are assembled together into a dosage form.

109.(New) A multi-component pharmaceutical dosage form which comprises a plurality of sub-units, each sub-unit being selected from

a) a drug substance-containing capsule compartment which is soluble or disintegrable in a patient's gastro-intestinal environment for release of the drug substance contained in the capsule compartment; and

b) a solid generally cylindrical body having an outer surface, the outer surface being exposed to a gastro-intestinal environment, the cylindrical body being composed of an extruded material comprising a pharmaceutical composition comprising:

a copolymer of methyl acrylate, methyl methacrylate and methacrylic acid, with molar ratio of monomer units of 7:3:1, and a ratio of free carboxyl groups to esters groups of 1:10, present in an amount of about 20 to 90% w/w,

at least two dissolution-modifying excipients selected from the group consisting of a swellable solid, disintegrant, non-reducing sugar, water soluble filler, wicking agent, and an inorganic salt present in an amount of about 2.5 to about 70% w/w,

a lubricant present in an amount of 10 to about 30% w/w,

and optionally a surfactant present in an amount of less than 5% w/w, a plasticizer present in an amount of 0 to 10% w/w, and/or a processing agent present in an amount of 0 to about 10% w/w,

wherein the pharmaceutical composition is substantially pH-independent;

and wherein the cylindrical body is comprised of the extruded material and is capable of time-controllably releasing the drug substance contained in the capsule compartment into the patient's gastro-intestinal environment, 4

and in which, at least prior to administration to a patient, the sub-units are assembled together into a dosage form.

Remarks

Claims 42, 44-47, 49-54 and 56-94, 96-109 are currently pending in this application. Claims 106-109 have been added. Claims 42, 50-52, 56, 71-90, 96, 99, 100, 102 and 104 have been amended with this amendment. Support for these amendments and newly added claims can be found throughout the specification and claims as originally filed, and no new matter is believed to be added by these amendments.

Rejection of claims under 35 U.S.C. §112

I. Rejection of claims 42, 44-47, 49-54, 56-105 under 35 U.S.C. §112, first paragraph as failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

The Examiner comments that he is unable to find "the claimed ratio for the copolymer of 7:3:1" in the specification. The claimed ratio is present in the data sheets supplied by the manufacturer which have been made of record. However, for the Examiners convenience Applicants enclose the data sheets for both Eudragit FS 30D and 41335F.

Applicants have further amended the claim to recite the ratio of free carboxyl groups to ester groups as shown in the manufacturer sheets for additional clarification.

II. Rejection of claim 42 under 35 U.S.C. §112, second paragraph as being non-enabling. Applicants respectfully traverse this rejection as well.

Claim 32 is stated to be indefinite as the Examiner is unclear "how a pharmaceutical dosage form can be pH independent, yet still be soluble, dispersible or disintegrable within a patient's acidic gastric environment and neutral to basic intestinal environment." (see Office Action, page 3, 1rst ¶).

The copolymer (referred to as 4135F) which is composed of methyl acrylate, methyl

methacrylate and methacrylic acid units, having a molar ratio of these monomer units of 7:3:1 is a polymer that the manufacturer Evonik refers to as being insoluble in acidic media, but dissolves by salt formation above pH 7.0. This is common for a polymer which is used for its enteric properties, e.g. coming off as a coating over a tablet in the colon as opposed to the stomach or the small intestines.

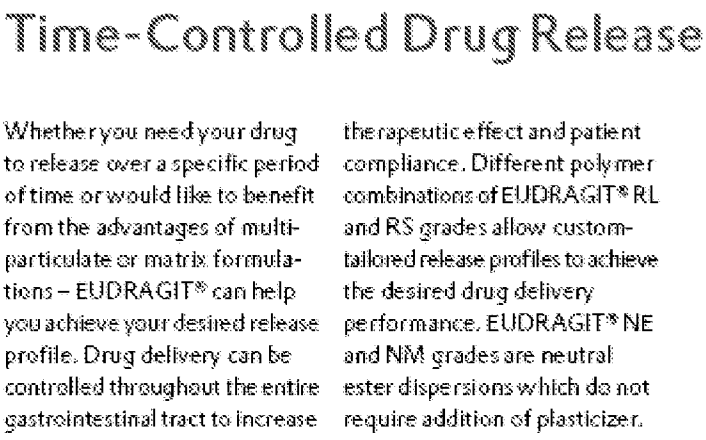
When a compound is said to be pH independent it is meant that the gastric environment does not affect the compound, otherwise they are referred to as pH dependent. The copolymer blend herein is no longer governed by the pH of the solution in the gastric tract, but dissolution/disintegration is time controlled release dependent instead.

Taking two extracts from the Evonik brochure on Eudragit coatings (shown below), one can readily see that you can have pH independent swellable materials. In other words, they can absorb water from the GI fluids but not necessarily dissolve. A copy of this brochure also accompanies this response.

A distinction is made between

1. Poly(meth)acrylates; soluble in digestive fluids by salt formation EUDRAGIT® L, S, FS and E polymers with acidic or alkaline groups enable pH-dependent release of the active ingredient.
Applications: from simple taste masking through gastric resistance to controlled drug release in all sections of the intestine

2. Poly(meth)acrylates; insoluble but permeable in digestive fluids EUDRAGIT® RL and RS polymers with alkaline and EUDRAGIT® NE polymers with neutral groups enable controlled time release of the active ingredient by pH-independent swelling.
Applications: delayed and sustained drug release



Time-Controlled Drug Release

Whether you need your drug to release over a specific period of time or would like to benefit from the advantages of multi-particulate or matrix formulations – EUDRAGIT® can help you achieve your desired release profile. Drug delivery can be controlled throughout the entire gastrointestinal tract to increase therapeutic effect and patient compliance. Different polymer combinations of EUDRAGIT® RL and RS grades allow custom-tailored release profiles to achieve the desired drug delivery performance. EUDRAGIT® NE and NM grades are neutral ester dispersions which do not require addition of plasticizer.

EUDRAGIT® Polymer	Availability	Dissolution Properties
RL 100	Granules	Insoluble
RL PO	Powder	High permeability
RL 30 D	30 % Aqueous Dispersion	pH-independent swelling
RL 12,5	12.5 % Organic Solution	
RS 100	Granules	Insoluble
RS PO	Powder	Low permeability
RS 30 D	30 % Aqueous Dispersion	pH-independent swelling
RS 12,5	12.5 % Organic Solution	
NE 30 D	30 % Aqueous Dispersion	Insoluble, low permeability,
NE 40 D	40 % Aqueous Dispersion	pH-independent swelling
NM 30 D	30 % Aqueous Dispersion	No plasticizer required Highly flexible

However, to advance prosecution on the merits applicants have removed the perhaps confusing terminology of "is soluble, dispersible or disintegrable in a patient's acidic gastric environment" from claim 42.

In view of these remarks and amendments, reconsideration and withdrawal of the rejection to the claims is respectfully requested.

Rejection of claims under 35 U.S.C. §103

I. Rejection of claims 42, 44-47, 49-54, 56-57, 59-80, 83, 85-91, 95-99, 102 and 103 under 35 U.S.C. §103(a) as being unpatentable over Petereit et al. (US 2002/0160042) in view of Adams et al. (US 6,139,875) for the reasons set forth previously is maintained.

II. Rejection of claims 42, 44-47, 49-54 and 56- 105 under 35 U.S.C. §103(a) as being unpatentable over Petereit, (US 2002/0160042) in view of Adams (US 6,139,875) and Hatano (US 6,309,666) for the reasons set forth previously is maintained.

Applicants traverse both of these rejections.

The Examiner's comments that "Applicants assertion that none of the references cited above teach a pharmaceutical composition which is substantially pH independent" is unclear as the claimed invention is inherent in that the same composition will have the same properties including its dissolution profile within a patients body. "Applicants have not amended their claims in such a way that the composition is materially different than the composition disclosed by the combination of references above. (See Office Action, page 4, 2nd and 3rd ¶).

It is clear from Applicants specification and the manufacturers own product that the claimed invention is in fact different from what is taught in the art, including the cited art herein. Applicants have adequately demonstrated pH independence of the copolymer in question. That pH independence could only have been achieved through the combination of specific excipients in the specific ranges as disclosed herein

Looking specifically at page 35 of the specification, lines 4-7 it is stated that the 4135F polymer "in its unformulated state is its high dissolution time, [is] in excess of 30 hours in aqueous media e.g. in SIF (simulated intestinal fluid). Therefore, to improve its dissolution time the polymer is blended with one or more hydrophilic excipients. This will enhance the absorption of water by the Eudragit 4135F polymer, and so accelerate the rate at which the blended polymer swells on absorption of water. As noted by the Experimental section herein, a dissolution modifying excipient, preferably a swellable solid excipient and optionally a second dissolution modifying excipient, such as a disintegrant, a lubricating agent, and if desired a surfactant, will produce a stable, injection molded component which can be reliably reproduced and injected from the mold with reduced, or no warpage of the shell."

The accompanying data provided throughout the working examples of the specification,

pages 38-49, and in particular pages 45-49 clearly demonstrate that these formulations as provided in molded subunits have a significant impact on the manner in which the polymer is behaves in the appropriate media. This is unexpected and not taught nor suggested by the prior art references.

The Examiner has commented that this advantage is not adequately provided for in the claims, however the independent claims all require the limitation "wherein the pharmaceutical composition is substantially pH-independent". As this is missing from the cited references, it is believed to distinguish the articles of manufacture herein. If the Examiner has a suggestion as to what further claim language is necessary, please let the undersigned know.

Petereit et al. does teach injection-molded capsules shells which are composed of varying methacrylate copolymers w/w percentages. In paragraph 0038 the FS grade copolymer (corresponding to 4135F herein) is noted as preferred. However, the Petereit reference does not teach a formulation of this specific copolymer in a multicomponent dosage form. The Petereit reference does not teach a formulation of this specific copolymer to produce a solid generally cylindrical bodies in combination with a capsule shell.

Petereit discloses formulation details to provide generically for the class of methacrylate copolymers but does not teach a formulation as claimed herein.

More specifically, Claim 42 and the other independent claims herein require the use of a lubricant present in an amount of about 10 to about 30% w/w. In contrast, the closest to this in the Petereit reference is the "release agents" in paragraph 0041 and 44 which are present in an amount of 0.1 to 3%, preferably 0.2 to 1% w/w based on the copolymer amounts.

Petereit does not teach nor suggest incorporation of a surfactant, such as those present in claim 45 herein. To the extent that the sorbitan fatty acid esters may be included within the context of an "ester of a fatty acid" (the specifics are not provided in Petereit), incorporation of this excipient is in addition to a lubricant in the formulation. The inclusion of both

excipients is not specifically provided for by Petereit. Petereit does not specifically teach nor suggest the particular surfactants, sodium dodecyl sulphate or is a block copolymer of ethylene oxide and propylene oxide, as claimed in claim 58 herein.

As noted previously as well, the admixture of a second polymer in the Petereit reference contains an error in paragraph 0080 whereby the term "hydroxypropylcellulose (HPMC)" is unclear. HPMC stands for hydroxypropylmethylcellulose and so it is unclear which polymer is actually being included. Applicants specifically require at least on dissolution modifying excipient (DME). One of the classes of a DME are those called "swellable solids". Within this class there are included "ethyl cellulose, cellulose acetate phthalate; hydroxypropyl cellulose, hydroxypropylmethyl cellulose, hydroxypropylmethyl cellulose phthalate, and other hydroxyalkylcellulose derivatives, and combinations or mixtures thereof." Petereit does not include more than one polymer as does the invention herein by use of the terminology "and combinations or mixtures thereof". Nor does Petereit "correctly" include these polymers.

Further, Applicants require in various claims herein, such as claim 94, a combination of two dissolution modifying excipients which are a swellable solid, hydroxypropylcellulose and a wicking agent, lactose. Petereit does not teach nor suggest such combinations.

Petereit does not teach nor suggest the other groupings of dissolution modifying excipients selected from a disintegrant, non-reducing sugar, water soluble filler, wicking agent, and an inorganic salt, such as presented in Claim 42, 47, 83, and 104, or the combination of two disintegrants as presented in claim 81.

Lastly, Petereit does not teach nor suggest the inclusion of at least two dissolution modifying excipients, as presented in Claim 80 which is a combination of specific disintegrants and swellable solids. Newly added Claims 108 and 109 are directed to the requirement of at least two dissolution modifying excipients, again, not taught nor suggested by Petereit.

Absent Applicants own specification there is no reason that the skilled artisan would be

directed to include a swellable solid in the formulation of Petereit. In the listing of copolymers in paragraph 0080, the vague and indefinite listing of HPC and/or HPMC is but one of a long listing of polymers which could be added to the mixture. There is no particular reason but for the teachings herein to pick and choose a swellable solid polymer that is hydroxypropylcellulose or hydroxypropylmethylcellulose from that listing.

The Examiner had cited in the prior Office Action, that the Adams reference teaches "an enteric composition comprising an enteric polymer, about 5 to 45 weight percent of a hydrophobic compound such as stearyl alcohol…"

The Examiner then on to state that "(a)s both references are drawn to enteric compositions, they are clearly within the same field of endeavor."

There is nothing in either the Adams reference to teach, or suggest that modification of the 4135F polymer with the specific excipients and amounts herein would change the polymer from a pH dependent polymer to a substantially pH independent polymer.

Hatano, directed to application of copolymer blends for enteric coating over capsule shells (not injection molding of the coating compositions) provides no additional teachings to direct the skilled artisan to incorporate the necessary excipients in the amounts as claimed herein. By definition, the enteric coatings used in Hatano are not pH independent. In fact, the use of methacrylate co-polymers and acrylic co-polymers in Hatano is to create an enteric coating on top of a low pH film layer on top of the hard capsule shell, with the enteric coating being soluble in a medium having a pH greater than 5 (col. 5, lines 60-64). Therefore, the enteric coating described by the Examiner clearly is pH dependent (in order to protect from solubilizing in the acidic gastric environment).

There is no teaching, suggestion, motivation or reason for one of ordinary skill in the art to use the teachings of Hatano and the other references to result in a substantially pH independent composition as in the present invention. Hatano does not make up for the deficiencies of Petereit and Adams with respect to changing the pH dependency of the

compositions described in those references, further exemplifies the unexpectedness of the presently claimed invention, since Hatano utilizes **two separate coatings, each having a different pH solubility** in order to provide the desired release profile.

The Examiner comments that the composition taught by the combination of references is within the same claimed scope of applicants claimed invention it is inherent that the same composition will have the same properties including its dissolution profile within a patient's body". This is simply incorrect.

It is only Applicants discovery that when the copolymer is admixed with the specifically claimed excipients in the specifically claimed amounts, extruded and injection molded that the resulting article of manufacture exhibits pH independence and the dissolution of the capsule relates to the time necessary to swell. This is unexpected.

As previously explained, the unexpectedness of the present invention is exemplified by an earlier Rohm patent filing, the Lehmann reference (US 5,709,189) (or record) which described numerous copolymers of methyl acrylate, methyl methacrylate and methacrylic acid formed into capsule shells and tested under both acidic and basic conditions. And under acidic conditions, no disintegration occurred (col. 5, lines 45 and 61-62), but under basic conditions, the capsule shells opened up (col. 5, lines 53 and 67). This means that the underlying composition which composed the article of manufacture were pH dependent, not pH independent.

This is a key distinction over the primary cited Petereit reference. In Petereit the polymers include 4135F, they are mixed with lubricant and/or plasticizer to produce moulded shells which when joined by means of cyanoacrylate adhesive provide a dosage form which is acid resistant but soluble in intestinal fluid. These shells are not pH-independent.

None of the references cited teach or suggest to the skilled artisan that modification of a copolymer blend would yield a substantially pH independent composition that can be injection molded into a multicomponent dosage form. None of these references teach the use

of such a composition to make injection molded subunits that can placed together in a dosage form and administered to a patient as in the claimed method herein (Claim 71). None of these teach the process of manufacture of a multicomponent dosage form as claimed herein (Claim 56).

In view of the failure of the references to even provide the necessary

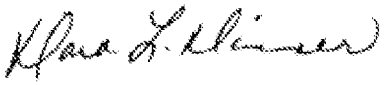
The amended claims are not prima facie obvious under 35 U.S.C. §103(a), and withdrawal of the rejection of these claims is respectfully requested.

Conclusion

As discussed above, the Examiner has not established a prima facie case of obviousness in view of Petereit in combination with any of the secondary references. The Applicants respectfully request the withdrawal of the rejection of the pending claims under 35 U.S.C. §103(a) and a prompt issuance of a Notice of Allowance.

Should the Examiner have any questions or wish to discuss any aspect of this application, the Examiner is encouraged to call the undersigned attorney at the number below.

Respectfully submitted,



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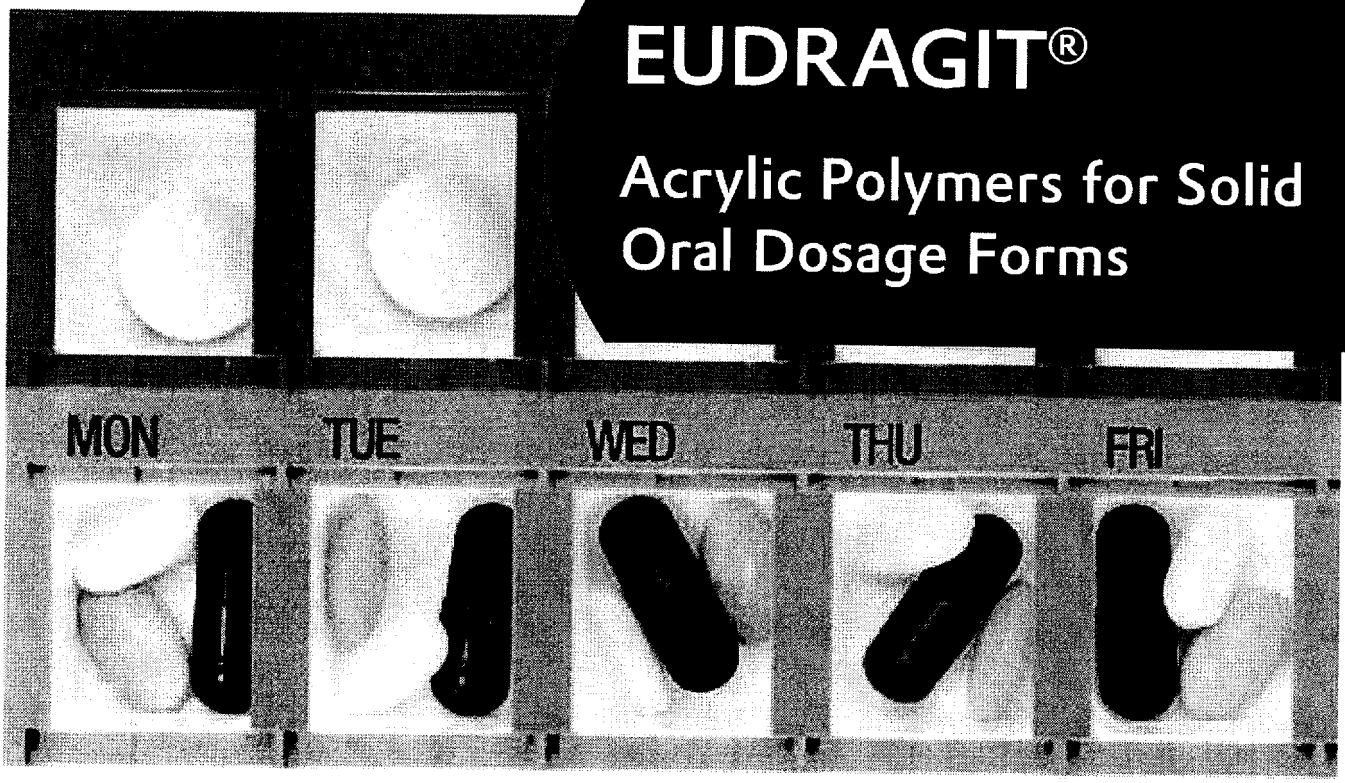
EVONIK
INDUSTRIES

EUDRAGIT®

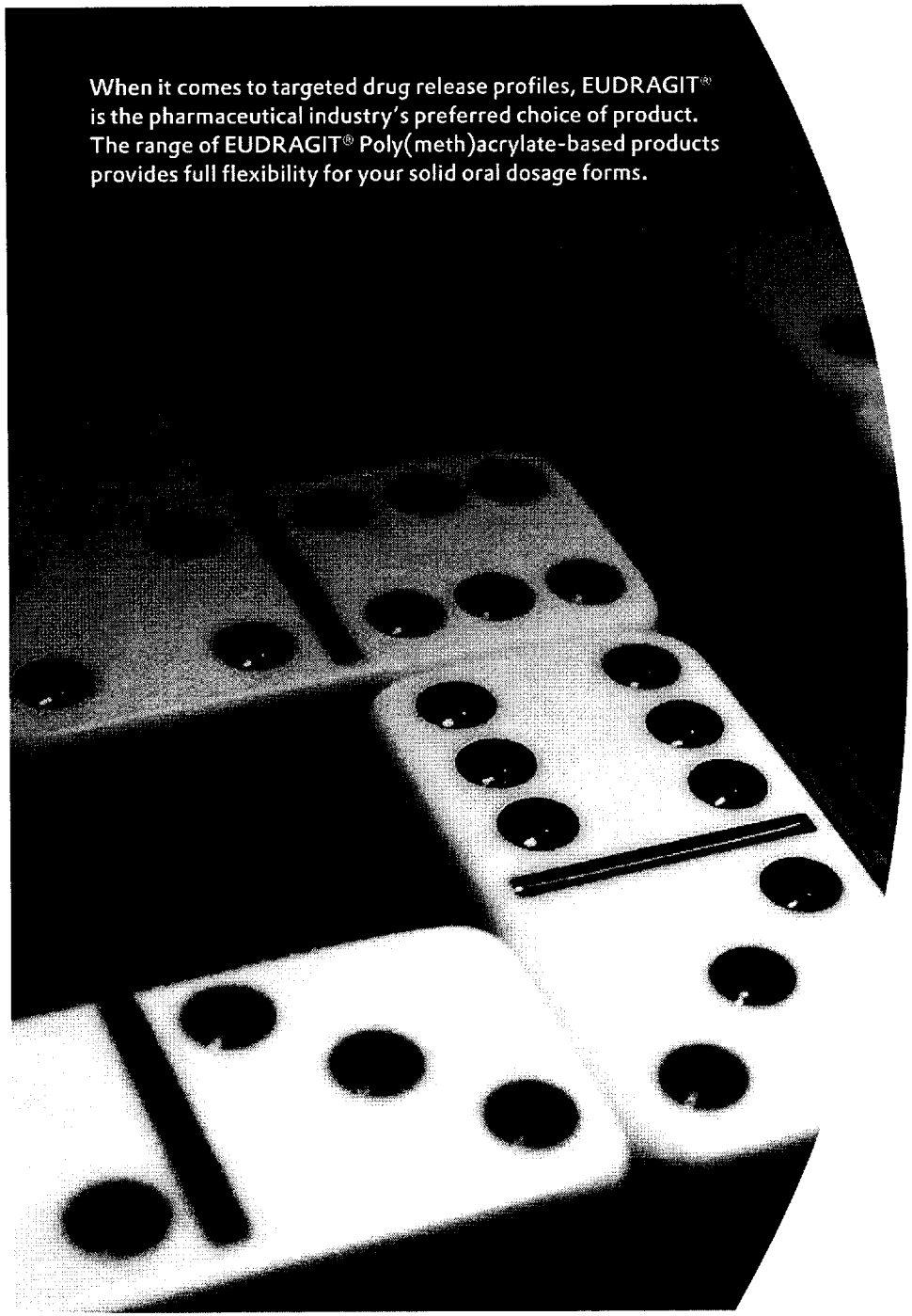
Acrylic Polymers for Solid Oral Dosage Forms



EUDRAGIT® Products → 2 Technical Support → 3 Formulation Development → 4 Proof of Concept → 5 GMP Services → 6 Drug Delivery & Licensing

Evonik. Power to create.

When it comes to targeted drug release profiles, EUDRAGIT® is the pharmaceutical industry's preferred choice of product. The range of EUDRAGIT® Poly(meth)acrylate-based products provides full flexibility for your solid oral dosage forms.



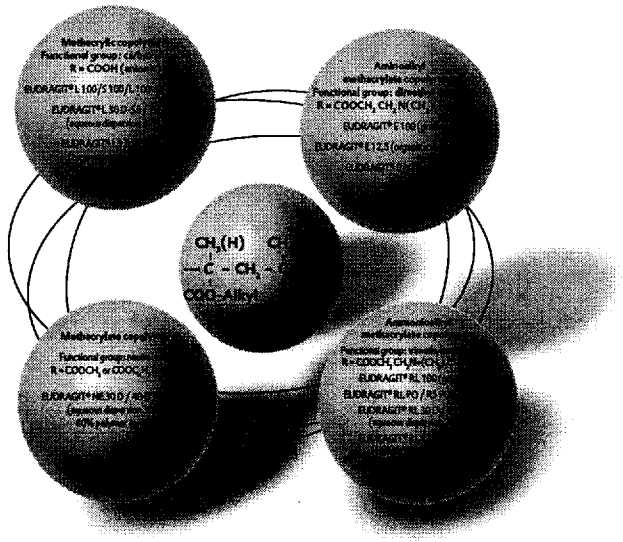
EUDRAGIT® Polymers – Pharmaceutical Properties

The basis of our offerings are our Poly(meth)acrylates for pharmaceutical applications, which are known worldwide in the industry under the trade name EUDRAGIT®. These polymers allow the active in your solid dosage form to perform during the passage of the human body. The flexibility to combine the different polymers enables you to achieve the desired drug release profile by releasing the drug at the right place and at the right time and, if necessary, over a desired period of time. Other important functions are protection from external influences (moisture) or taste/odor masking to increase patient compliance. The range of our product portfolio provides full flexibility for your targeted drug release profiles by offering best performance for enteric, protective or sustained-release properties.

EUDRAGIT® polymers are copolymers derived from esters of acrylic and methacrylic acid, whose physicochemical properties are determined by functional groups (R). EUDRAGIT® polymers are available in a wide range of different physical forms (aqueous dispersion, organic solution granules and powders).

A distinction is made between
1. Poly(meth)acrylates; soluble in digestive fluids by salt formation EUDRAGIT® L, S, FS and E polymers with acidic or alkaline groups enable pH-dependent release of the active ingredient.
Applications: from simple taste masking through gastric resistance to controlled drug release in all sections of the intestine

2. Poly(meth)acrylates; insoluble but permeable in digestive fluids EUDRAGIT® RL and RS polymers with alkaline and EUDRAGIT® NE polymers with neutral groups enable controlled time release of the active ingredient by pH-independent swelling.
Applications: delayed and sustained drug release



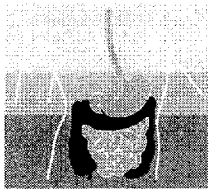
EUDRAGIT® offers valuable advantages for your enteric coatings:

- PH-dependent drug release
- Protection of actives sensitive to gastric fluid
- Protection of gastric mucosa from aggressive actives
- Increase in drug effectiveness
- Good storage stability
- GI and colon targeting

Gastroresistance and GI Targeting

If you need to protect your active from the gastric fluid and would like to improve drug effectiveness – EUDRAGIT® L and S polymers are your preferred choice of coating polymers. They enable targeting specific areas of the intestine. Pharma Polymers offers a broad product portfolio of anionic EUDRAGIT® grades which dissolve at rising pH values. In addition, the different grades can be combined with each other, making it possible to adjust the dissolution pH, and thus to achieve the required GI targeting for the drug.

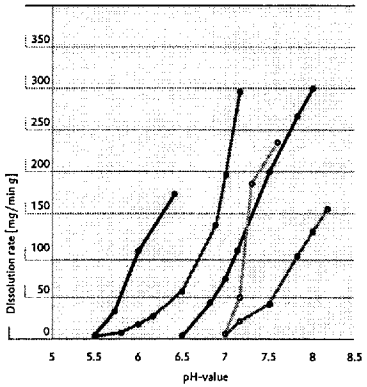
EUDRAGIT® Polymer	Availability	Dissolution Properties
L30D-55	30% Aqueous Dispersion	Dissolution above pH 5.5
L100-55	Powder	
L100	Powder	Dissolution above pH 6.0
L 12,5	12.5% Organic Solution	
S100	Powder	Dissolution above pH 7.0
S 12,5	12.5% Organic Solution	
FS 30 D	30% Aqueous Dispersion	

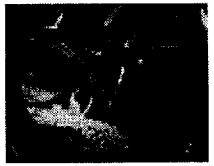


Targeted drug release in the colon is required for local treatment of intestinal disorders such as Crohn's disease, ulcerative colitis or intestinal cancer. It is also required for drugs that are poorly soluble in the upper gastrointestinal tract. Moreover, the gastroresistance of the coating ensures that the oral dosage form is patient compliant.

The preferred coating is EUDRAGIT® FS 30 D, which combines release in the colon with the following technical advantages:

- aqueous processing
- highly flexible coatings
- suitable for multiparticulate tablet preparation





Our protective polymers are suitable for aqueous or organic coatings and can be applied in a melt extrusion process. During the melt extrusion process the cationic EUDRAGIT® E polymer interacts with the anionic active which provides excellent taste masking properties.

Moisture Protection and Odor/Taste Masking

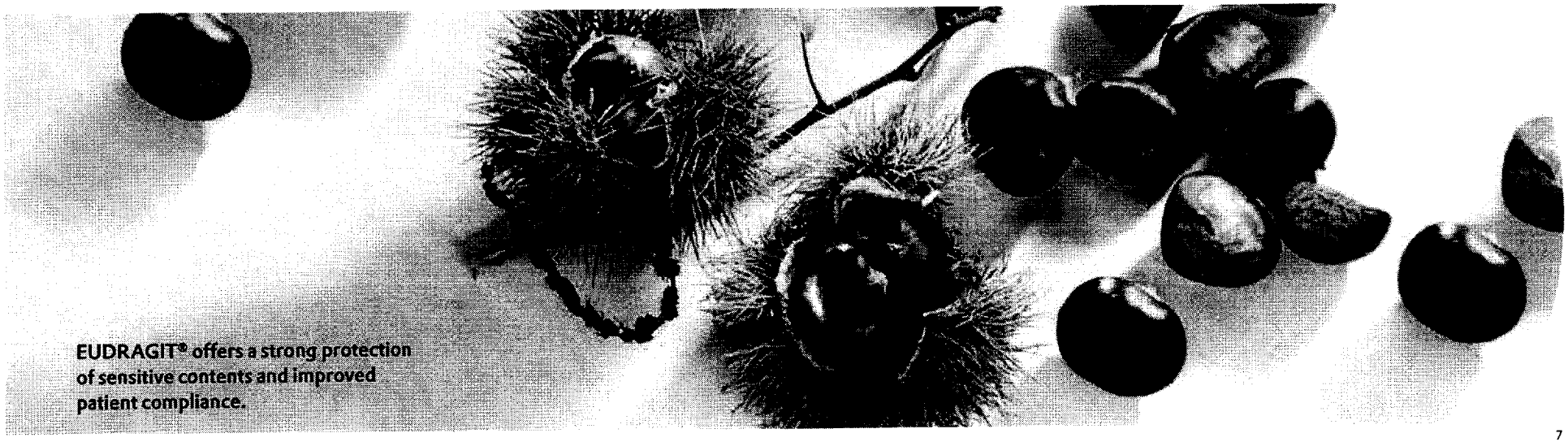
Do you need to protect your active from moisture or light and would like to increase patient compliance?

EUDRAGIT® E polymers help you to seal sensitive actives and increase patient compliance by masking tastes and odors. Even thin layers of EUDRAGIT® provide the desired effect, making it an extremely economical application. Pharma Polymers offer various cationic EUDRAGIT® E grades for protective coatings.

EUDRAGIT® Polymer	Availability	Dissolution Properties
E100	Granules	Soluble in gastric fluid up to pH 5.0
E12,5	12.5% Organic Solution	Swellable and permeable above pH 5.0
EPO	Powder	

Take advantage of protective EUDRAGIT® coatings:

- pH-dependent drug release
- Protection of sensitive actives
- Taste and odor masking
- Moisture protection
- Economical application
- Improved passage of the dosage form
- Smooth and glossy surfaces, good color coating

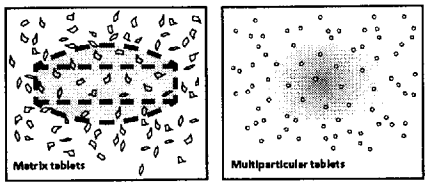


EUDRAGIT® offers a strong protection of sensitive contents and improved patient compliance.

Time-Controlled Drug Release

Whether you need your drug to release over a specific period of time or would like to benefit from the advantages of multi-particulate or matrix formulations – EUDRAGIT® can help you achieve your desired release profile. Drug delivery can be controlled throughout the entire gastrointestinal tract to increase therapeutic effect and patient compliance. Different polymer combinations of EUDRAGIT® RL and RS grades allow custom-tailored release profiles to achieve the desired drug delivery performance. EUDRAGIT® NE and NM grades are neutral ester dispersions which do not require addition of plasticizer.

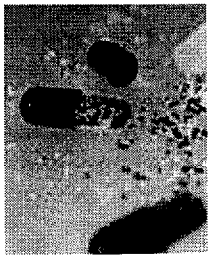
EUDRAGIT® Polymer	Availability	Dissolution Properties
RL 100	Granules	Insoluble
RL PO	Powder	**High permeability**
RL 30 D	30% Aqueous Dispersion	pH-independent swelling
RL 12,5	12.5% Organic Solution	
RS 100	Granules	Insoluble
RS PO	Powder	**Low permeability**
RS 30 D	30% Aqueous Dispersion	pH-independent swelling
RS 12,5	12.5% Organic Solution	
NE 30 D	30% Aqueous Dispersion	Insoluble, low permeability,
NE 40 D	40% Aqueous Dispersion	pH-independent swelling
NM 30 D	30% Aqueous Dispersion	**No plasticizer required** Highly flexible



There are two formulation options:

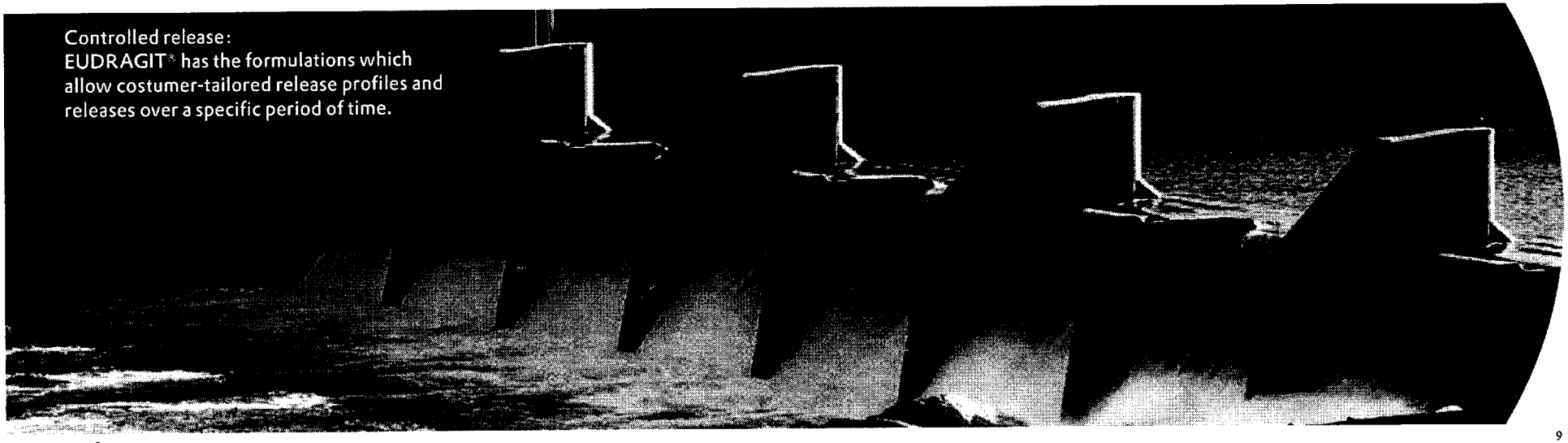
EUDRAGIT® serves as a matrix within which the active ingredient is embedded. The matrix structure is obtained by direct compression, granulation, or melt extrusion. EUDRAGIT® NM 30 D is particularly suitable for granulation processes in the manufacture of matrix tablets.

EUDRAGIT® is employed as a coating material, usually for the coating of pellets or particles that are filled into capsules or compressed into tablets. These pellets or particles act as diffusion cells in the digestive tract and release a constant drug quantity per unit of time (multi-unit dosage forms).



Benefit from EUDRAGIT® coatings with sustained release:

- Time-controlled release of active ingredients
- Therapeutically customized release profiles
- Higher patient compliance due to reduced number of doses to be taken
- Cost-effective processing



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Evonik. Power to create.

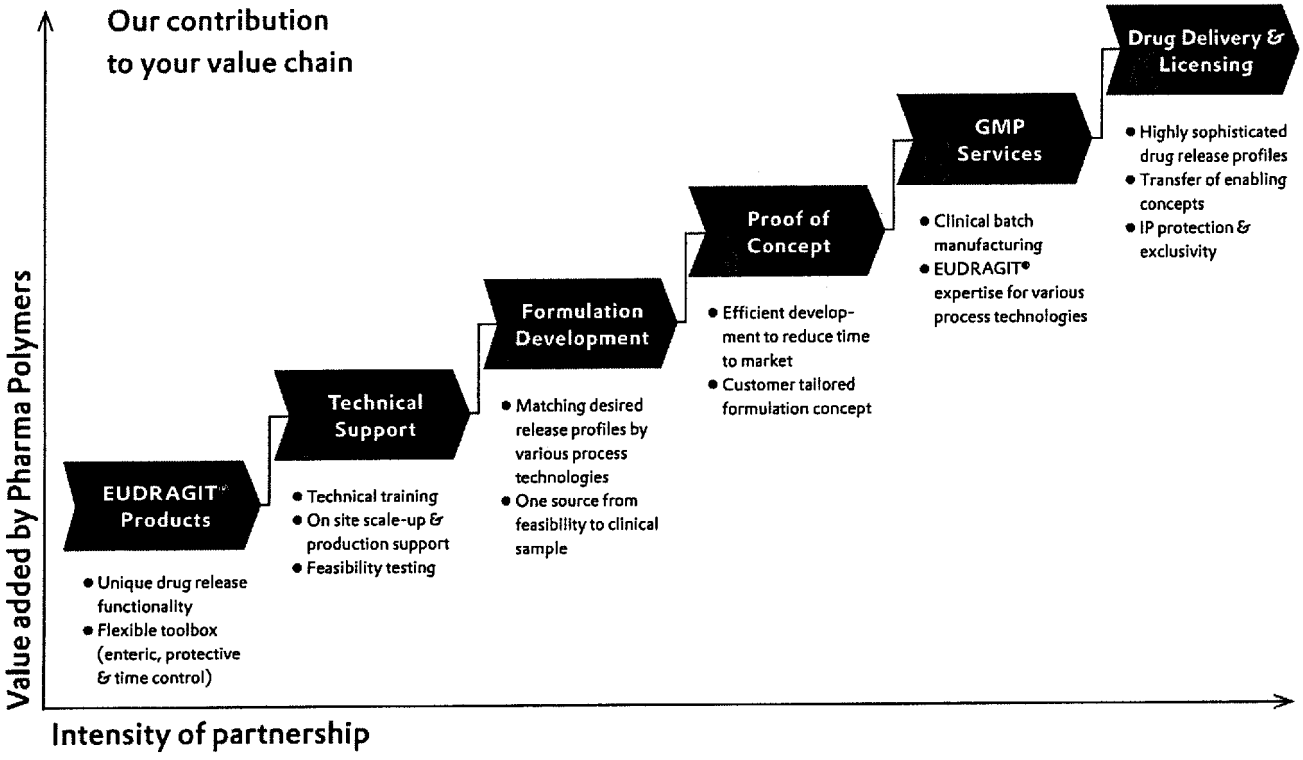
Market Strength by means of Strategic Partnership

Pharma Polymers, a business line of Evonik Industries, offers the complete line of EUDRAGIT® products and related services along the value chain of our customers. For over 50 years we have proven our reliability as a quality partner to the pharmaceutical industry. Our state of the art services cover various stages of the development processes, including

- advanced technical support
- formulation development
- proof of concept
- GMP services.

Our customers see us as a strategic partner for their developments of solid oral dosage forms with a targeted drug release profile. By using our value adding business model our customers get:

- increased efficiency in their R&D and manufacturing processes
- new drug delivery technologies
- reduction of the time to market for their developments
- professional management of their product's life cycle



degussa.

Röhm Pharma Polymers

Preliminary specifications, test methods and processing characteristics for Präparat 4135 F (Preparation 4135 F)

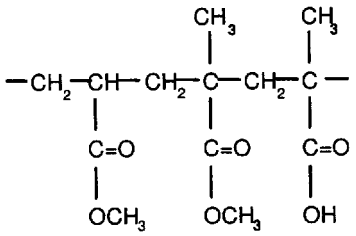
Preliminary specifications

1 Commercial form

Solid substance obtained from EUDRAGIT® FS 30 D by stress coagulation and extrusion, the product contains small amounts of Sodium Laurylsulfate Ph. Eur. / NF. and Polysorbate 80 Ph. Eur. / NF.

2 Chemical structure

Präparat 4135 F is a copolymer of methyl acrylate, methyl methacrylate and methacrylic acid.



The ratio of the free carboxyl groups to the ester groups is approx. 1:10.
The average molecular weight is approx. 220,000.

3 Characters

Description

Colourless to yellow tinged granules with a faint characteristic odour

Solubility

1 g of Präparat 4135 F dissolves in 7 g aqueous acetone (H_2O 3% w/w) to give a clear solution or in 7 g 1 N sodium hydroxide solution to give a slightly cloudy solution.
The solid substance is practically insoluble in petroleum ether.

4 Tests

Dry substance (DS)

Not less than 97 %.
According to Ph.Eur. "Loss on drying", method d, approx. 1 g of the granules is dried for 3 hours at 110°C.

Assay

9.2 – 12.3 % methacrylic acid units on dry substance (DS)

Acid value: 60 - 80 mg KOH per g of dry substance

The assay is performed according to Ph. Eur. "Potentiometric titration" or USP <541>.
Approx. 2.0 g of Präparat 4135 F are dissolved in 90 ml isopropyl alcohol and 10 ml water.
Titration is performed with 0.5 N sodium hydroxide (NaOH).
A blank value is determined under the same conditions.
1 ml 0.5 N NaOH corresponds to 43.045 mg methacrylic acid units.

$$\text{Methacrylic acid units (\%) on DS} = \frac{\text{ml 0.5 N NaOH} \cdot 430.45}{\text{sample weight (g)} \cdot \text{DS (\%)}}$$

The acid value (AV) states how many mg KOH are required to neutralize the acid groups contained in 1 g dry substance.

AV (mg KOH / g DS) = methacrylic acid units (%) · 6.517

5 Purity

Sulphated ash / Residue on ignition

Max. 0.2 % according to Ph. Eur. 2.4.14 or USP <281>.
1 g Präparat 4135 F is used for the test

Heavy metals

Max. 20 ppm according to Ph. Eur. 2.4.8 method C or USP <231> method II.
1 g Präparat 4135 F is used for the test.

Monomers

Max. 500 ppm, determined by means of liquid chromatography according to Ph. Eur. 2.2.29 or USP <621>.

Sample solution:
Dissolve 1.00 g of Präparat 4135 F in acetone p.a. and dilute to 50.0 ml.
Add 10.0 ml of the solution drop wise to 40 ml of a 70 % solution of methanol for chromatography in water. Centrifuge for 5 min at 6000 rpm and use the supernatant solution as the test solution.

Reference solutions:
Pipette 10.0 mg of methyl acrylate to 5 ml of iso-butanol and dilute to 50.0 ml with acetone p.a. Dilute 1.0 ml of the solution to 100.0 ml with acetone p.a. Take 10.0 ml of this solution and mix with 40 ml of a 70% solution of methanol for chromatography in water. Pipette 10.0 mg of methacrylic acid and 10.0 mg of methyl methacrylate to 5 ml of iso-butanol and dilute to 50.0 ml with acetone p.a. Dilute 1.0 ml of the solution to 100.0 ml with acetone p.a. Take 10.0 ml of this solution and mix with 40 ml of a 70 % solution of methanol for chromatography in water.

Procedure: The chromatographic procedure may be carried out using:
- a column 120 mm long and 4.6 mm in internal diameter packed with octadecylsilyl silica gel for chromatography R (7 µm) Ph. Eur. (USP: L1),
- as mobile phase at a flow rate of 2 ml per minute a mixture of 20 volumes of methanol R and 80 volumes of phosphoric acid pH 3.8,
- as detector a spectrophotometer set at 200 nm.

Inject separately equal volumes (about 20 µl) of each solution.

Calculate the content of monomers from the height of the peaks in the chromatograms obtained with the sample solution and the reference solutions, from the content of monomers in the reference solutions and from the sample weight.

Microbial count
Max. 1,000 CFU / g; Salmonella not detectable in 10 g, E. coli, S. aureus, Ps. aeruginosa not detectable in 1 g. The test is performed according to Ph. Eur. 2.6.12 and 2.6.13.

6 Identity testing

Proof of identity is furnished by IR spectroscopy on a dry film of Präparat 4135 F approx. 15 µm thick.

To obtain the film, some drops of an approx.10 - 15 % solution of Präparat 4135 F in acetone is placed on a crystal disc of KBr and dried in vacuum for about 2 hours at 70 °C.

The location and intensity of the bands correspond to Figure 1.
The figure shows the characteristic band of the C = O vibrations of the esterified carboxyl groups at 1732 cm^{-1}, which overlaps the band of the C = O vibrations of the carboxylic acid groups at 1705 cm^{-1}. Further ester vibrations are detected at 1166, 1196, 1235 and 1263 cm^{-1}. The wide absorption range of associated OH Groups between 2500 and 3500 cm^{-1} is superimposed by CH_X vibrations at 2900 – 3000 cm^{-1}. Further CH_X vibrations can be discerned at 1386, 1439 and 1447 cm^{-1}.

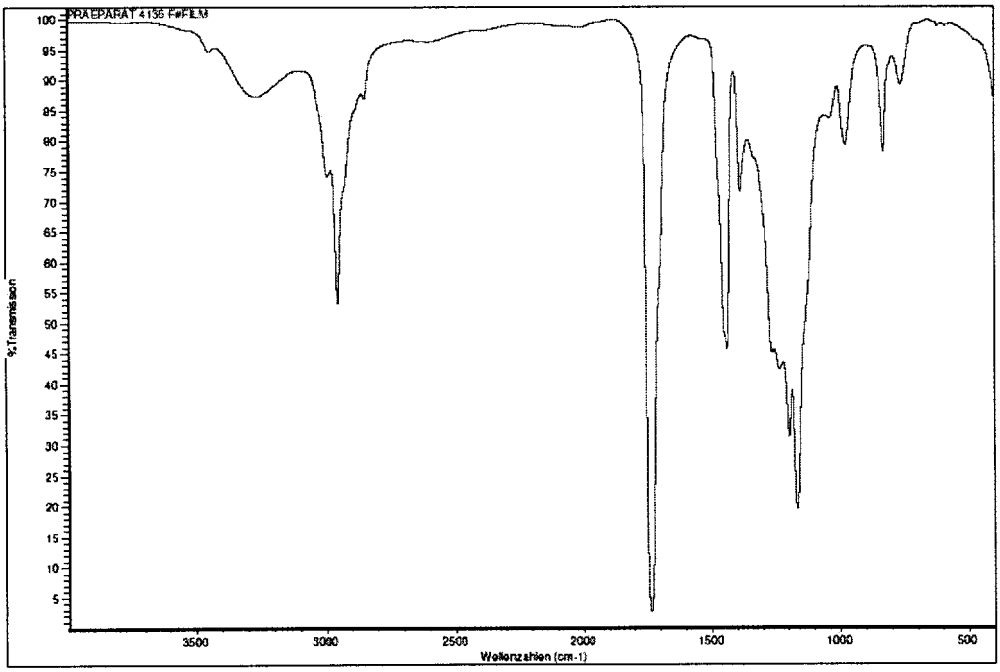


Figure 1: IR spectrum of Präparat 4135 F

7. Storage and handling:

Protect from warm temperature (USP, General Notices)
Protect from moisture.

8. Stability:

Storage stability data are available upon request.

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EVONIK INDUSTRIES

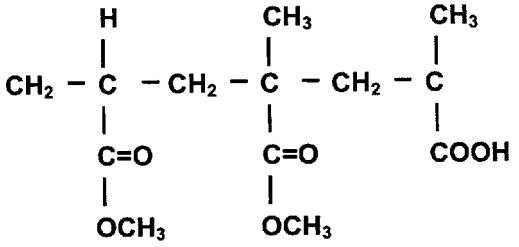
EUDRAGIT® FS 30 D

A versatile polymer for controlled release applications

- Aqueous polymer dispersion
- Dissolution > pH 7.0
- Highly flexible
- Suitable for multi unit dosage forms
- pH independent matrix structures
- Miscible with other EUDRAGIT® polymers to enhance flexibility or adjust specific drug release

Chemical properties

EUDRAGIT® FS 30 D is the aqueous dispersion of an anionic copolymer based on methyl acrylate, methyl methacrylate and methacrylic acid. It is insoluble in acidic media, but dissolves by salt formation above pH 7.0. Apart from its enteric properties, its dissolution at a higher pH value allows targeted colon delivery.



With a glass transition temperature of 48 °C, EUDRAGIT® FS 30 D is a very flexible polymer. Due to the low minimum film forming temperature only small amounts of plasticizer are required to get a smooth film formation.

Properties

Soluble	> pH 7.0
Tg	~ 48 °C
MFT	~ 14 °C
Molecular weight	~ 220,000

Tablet coating

This example formulation was calculated for the coating of 37,900 g tablets (w 300 mg, h 4 mm, d 10 mm).

A spray suspension of EUDRAGIT® FS 30 D can be prepared by using talc or glycerol monostearate (GMS) as glidant. The advantage of using GMS is that the total applied solids are only 70% of the talc formulation. The reason is that only 5% of GMS have to be used instead of 50% of talc.

Example formulation for tablet coating with glycerol monostearate as glidant

		Solids	On Dry polymer
EUDRAGIT® FS 30 D	5,953 g	1,786 g	
GMS	89 g	89 g	5%
Polysorbat 80 (33% aqu.)	108 g	36 g	40% on GMS
TEC	89 g	89 g	5%
Water	3,761 g	---	
Total	**10,000 g**		

Solid content: 20.0%
Polymer content: 17.8%
Applied polymer: 5.0 mg/cm²
Applied total solids: 5.6 mg/cm²

pH independent matrix tablets

EUDRAGIT® FS 30 D provides a pH independent diffusion based matrix tablet under non polymer dissolving conditions. The matrix stays intact during its way through the GI tract and releases the drug diffusion controlled. Late in the colon the matrix will dissolve completely. That ensures a 100% drug release.

Example formulation for pH independent matrix tablets

		Solids	% of tablet
Granules	Diltiazem	1,450 g	29.0 %
	Emcompress®	2,695 g	53.9 %
	EUDRAGIT® FS 30 D*	830 g	16.6 %
Tablet	Mg stearate	25 g	0.5 %
Total		**5,000 g**	**100.0%**

* stated as solid

A polymer amount of 10 to 20% is sufficient to get a pH independent drug release.

Adjustment of dissolution pH by mixing of different polymer types

Many pharmaceutical actives require release at specific pH values in order to find best absorption conditions in the GI tract.
The mixing ratio of EUDRAGIT® FS 30 D & EUDRAGIT® L 30 D-55 can be used to adjust the release of a dosage form in a pH range from pH 6.0 to pH 6.8. An additional control element is partial neutralization of the polymer carboxylic groups, which increases the dissolution speed.

Using this 2 factor tool box, film coatings to fulfill the specific needs of various drugs can be developed easily.

More information on that topic can be found on our latest CRS poster: "Accurate GI Targeting with EUDRAGIT® FS 30 D/ L 30 D-55 mixtures", presented at CRS 2008 in New York City.

Summary of product advantages

- **A solubility above pH 7.0 allows specific colon targeting**
- **Because of its flexibility it is particularly suitable for multi unit dosage forms**
- **Matrix systems based on EUDRAGIT® FS 30 D ensures a 100% drug release.**
- **Polymer amounts of 10 to 20% are sufficient to get a pH-independent matrix**
- **The flexibility of EUDRAGIT® FS 30 D makes this polymer particularly suitable for the mixing with EUDRAGIT® L 30 D-55.**
- **Amounts below 50% do only influence the flexibility of the EUDRAGIT® L 30 D-55 coating, not the release profile. With amounts > 75% specific sites in the GI tract can be targeted**

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EVONIK INDUSTRIES

Specifications and test methods for

EUDRAGIT® FS 30 D

Specification

1 Commercial form

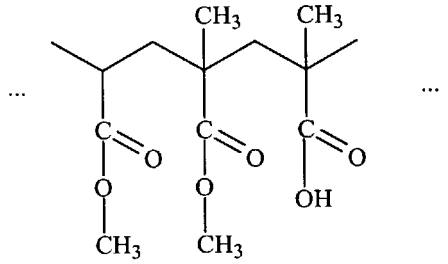
Aqueous dispersion with 30 % dry substance

The water is tested according to the specifications of "Purified Water in bulk" Ph. Eur. and according to the specifications for Conductivity of "Purified Water" USP.

The dispersion contains 0.3 % Sodium Laurilsulfate Ph. Eur. / NF and 1.2 % Polysorbate 80 Ph. Eur. / NF on solid substance, as emulsifiers.

2 Chemical structure

EUDRAGIT® FS 30 D is the aqueous dispersion of an anionic copolymer based on methyl acrylate, methyl methacrylate and methacrylic acid.



The ratio of the free carboxyl groups to the ester groups is approx. 1:10.
The average molecular weight is approx. 220,000.

3 Characters

Description

Milky-white liquid of low viscosity with a faint characteristic odour.

Solubility

The dispersion is miscible with water in any proportion, the milky-white appearance being retained. A clear or slightly cloudy, viscous solution is obtained by mixing 1 part EUDRAGIT® FS 30 D with 5 parts acetone. The same results are obtained by mixing with ethanol or isopropyl alcohol; initially, the polymer is precipitated, but then dissolves again in the excess organic solvent.
A clear or slightly cloudy liquid is obtained by mixing 1 part EUDRAGIT® FS 30 D with 2 parts 1 N sodium hydroxide.

4 Tests

Film formation

10 g EUDRAGIT® FS 30 D are mixed with 0.3 g triethyl citrate. When the dispersion is poured onto a glass plate, a cloudy film forms upon evaporation of the water.

Dry substance / Residue on evaporation

28.5 - 31.5 %
1 g of the dispersion is dried in an oven for 5 hrs at 110 °C, according to Ph. Eur. 2.2.32 method d. The dispersion must form a clear film after drying.

Assay

9.2 – 12.3 % methacrylic acid units on dry substance (DS)
Acid value: 60 – 80 mg KOH per g DS
The assay is performed according to Ph. Eur. 2.2.20 "Potentiometric titration" or USP <541>.

5.0 g EUDRAGIT® FS 30 D are dissolved in 90 ml isopropyl alcohol and 10 ml water. Sodium hydroxide (NaOH) 0.5 N is used as the titrant. Under the same conditions, a blank value is determined. 1 ml 0.5 N NaOH corresponds to 43.045 mg methacrylic acid units.

$$\text{Methacrylic acid units (\%) on DS} = \frac{\text{ml 0.5N NaOH} \cdot 430.45}{\text{sample weight (g)} \cdot \text{DS (\%)}}$$

The acid value (AV) states how many mg KOH are required to neutralise the acid groups contained in 1 g dry substance.

Viscosity / Apparent viscosity

Max. 20 mPa · s
The viscosity of the dispersion is determined by means of a Brookfield viscometer (UL adapter / 30 rpm / 20 °C).

pH

2.0 - 3.5
The pH is determined according to Ph. Eur. 2.2.3.

Relative density

d_{20}^{20}: 1.058 - 1.068
The relative density is determined according to Ph. Eur. 2.2.5.

Coagulum content

Max. 1,000 mg / 100 g
A stainless steel wire cloth with a mesh size of 0.09 mm (mesh number 90, ISO) is accurately weighed. 100 g EUDRAGIT® FS 30 D are filtered through this cloth, which is then washed with water until a clear filtrate is obtained, dried to constant weight at 105 °C and weighed to determine the filtration residue.

5 Purity

Sulphated ash / Residue on ignition

Max. 0.2 %
The test is performed according to Ph. Eur. 2.4.14 or USP <281>.
1 g EUDRAGIT® FS 30 D is used for the test.

Heavy metals

Max. 20 ppm
The test is performed according to Ph. Eur. 2.4.8 method C or USP <231> method II.
1 g EUDRAGIT® FS 30 D is used for the test.

Monomers

Max. 100 ppm, determined by liquid chromatography according to Ph. Eur. 2.2.29 or USP <621>.

Sample solution: Dissolve approximately 11.0 g accurately weighed of EUDRAGIT® FS 30 D in acetone p.a. and dilute to 50.0 ml. Add 5.0 ml of the solution dropwise to 20 ml of a 70 % solution of methanol for chromatography in phosphoric acid pH 2 (adjust an appropriate volume of water with Phosphoric acid 85 % to pH 2). Centrifuge until the supernatant is clear and use the supernatant solution as the sample solution.

Reference solution:
Pipette approximately 11 mg of methacrylic acid, 10 mg of methyl acrylate and 12 mg of methyl methacrylate, each accurately weighed, to 5 ml of iso-butanol and dilute to 50.0 ml with acetone. Dilute 5.0 ml of the solution to 50.0 ml with acetone. Dilute 20.0 ml of the solution to 50.0 ml with acetone. Take 5 ml of this solution and mix with 20 ml of a 70:30 mixture of methanol for chromatography and phosphoric acid pH 2.

Procedure: The chromatographic procedure may be carried out using:
- a column 125 mm long and 4.6 mm in internal diameter packed with octadecylsilyl silica gel for chromatography R (7 µm). (USP: L1. i.e. Nucleosil 100-7 µm, C18),
- as mobile phase at a flow rate of 2 ml per minute a 10 : 90 mixture of acetonitrile p.a. and phosphoric acid pH2
- as detector a spectrophotometer set at 200 nm.

Separately inject equal volumes (about 20 µl) of the sample solution and the reference solution.

Calculate the content of monomers from the area of the peaks in the chromatograms obtained with the sample solution and the reference solution, from the content of monomers in the reference solution and from the sample weight and the dilution factor.

Residual Solvents / Organic Volatile Impurities

Organic solvents are not used in the manufacture, packing and storage of this product.

Small amounts of methanol may be detectable in this product after longer storage.
The concentration is below 0.1 %.
The test is performed according to Ph. Eur. 2.4.24, sample preparation 2.

Microbial count

Total aerobic microbial count (TAMC): max. 1,000 CFU / g
Total combined yeasts and moulds count (TYMC): max. 100 CFU / g
(Acceptance criteria according to Ph. Eur. 5.1.4 / USP 1111)
The test is performed according to Ph. Eur. 2.6.12 or USP <61>.

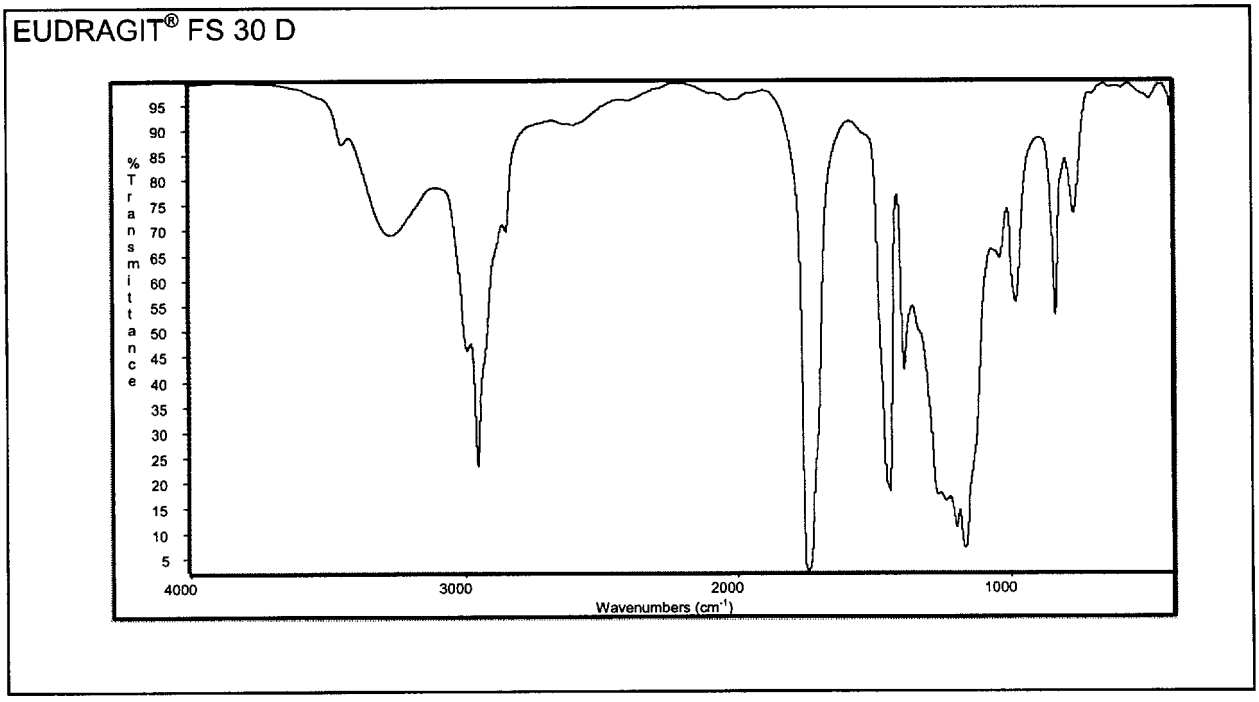
6 Identity testing

First identification

The material must comply with the tests for "Assay" and "Viscosity / Apparent viscosity."

Second identification

IR spectroscopy on a dry film approx. 15 µm thick. The film is obtained by applying one drop of EUDRAGIT® FS 30 D to a glass plate and covering with a water-resistant crystal disc (AgCl, KRS 5). By lightly pressing on and then removing the crystal disc, a clear film is obtained after a drying period of about 15 minutes at 60 °C.
The figure on page 4 shows the characteristic band of the C = O vibrations of the esterified carboxyl groups at 1732 cm^{-1}, which overlaps the band of the C = O vibrations of the carboxylic acid groups at 1705 cm^{-1}. Further ester vibrations are detected at 1166, 1196,1235 and 1263 cm^{-1}. The wide absorption range of associated OH Groups between 2500 and 3500 cm^{-1} is superimposed by CH_X vibrations at 2900 – 3000 cm^{-1}. Further CH_X vibrations can be discerned at 1386, 1439 and 1447 cm^{-1}.



7 Detection in dosage forms

The dosage forms are extracted using the solvents listed under "Solubility," if necessary after crushing. Insoluble substances are isolated by filtration or centrifugation. The clear filtrate is boiled down and the residue identified by IR spectroscopy.

8 Storage and handling

Store between 5 °C and 10 °C. Protect from freezing. Keep in well closed containers.

Avoid contamination during sampling. Containers that have been opened for use should be closed again immediately and the content used up within the next few weeks.

9 Stability

Minimum stability dates are given on the product labels and batch-related Certificates of Analysis. Storage stability data are available upon request.

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Product Profile
EUDRAGIT® FS 30 D

Question	Answer	Remarks / Further Information
Chemical name	Polymer: Poly(methyl acrylate-co-methyl methacrylate-co-methacrylic acid) 7:3:1 (220,000)	IUPAC name
Pharmacopeial names		The product is not yet described in a pharmacopoeial monograph.
Confirmation of Suitability of Ph. Eur.	Not applicable	
INCI name	Acrylates Copolymer	
Regulatory Status for use in Food	USA: not approved as direct or as indirect food additive (21 CFR 172 to 177 and 180 to 186) EU: not listed (Council Directive 89/107/EEC and amendments)	Available upon request
Name and Address of the manufacturer	EVONIK Röhm GmbH Kirschenallee D-64293 Darmstadt Tel: +49 (0) 6151 18-01 Fax: +49 (0) 6151 18-3555 www.pharma-polymers.com	
Country of origin	Germany	
Contact information	Concerning this questionnaire:	Dr. Johanna Eisele Regulatory Affairs Tel: +49 (0) 6151 18-4763 E-mail: Johanna.Eisele@evonik.com
	Sales/Purchasing:	Mr. Karsten Weber Customer Service Tel: +49 (0) 6151 18-3550 E-mail: Karsten.Weber@evonik.com
Quality policy	GMP for Bulk Pharmaceutical Excipients (BPE); USP/NF <1078>	The Joint IPEC – PQG Good Manufacturing Guide for BPE
	ISO 9001	DIN ISO 9001 Certificate
Environmental policy	ISO 14001	DIN ISO 14001 Certificate; Environmental Protection, Safety, Health and Quality Policy of EVONIK Röhm GmbH (enclosed)

Question	Answer	Remarks / Further Information
Supplier rating system	Yes, by incoming quality control and auditing	
Self-auditing system	Operating	
Auditing by customers	Yes	Approx. 10 audits/year
Auditing by regulatory bodies	Regierungspräsidium Darmstadt	For chemical and pharmaceutical production
History of product use in pharmaceuticals	Year of Introduction: 1999	Available upon request
Kosher certification	No	Animal derived raw materials are not used in the manufacture
Halal certification	No	Animal derived raw materials are not used in the manufacture
Production process	Chemical synthesis: Emulsion polymerization and filtration	Production Flow Chart (enclosed)
Source of raw materials	Chemical	
Is the material sterilized?	No	
Minimum stability date	See Certificate of Analysis and product label	Stability data available upon request
Storage conditions	See Specification leaflet and product label	INFO 7.12/E (enclosed)
Testing methods	See Specification leaflet	INFO 7.12/E
Residual solvents (formerly: Organic Volatile Impurities)	Organic solvents are not used in the manufacture, packing and storage of this product. Small amounts of ***Methanol*** and **Ethanol** may be detectable in this product within the minimum stability period. The concentration remains ***below 0.1 %*** and **below 0.5 %**, respectively.	USP <467> Residual solvents; ICH Residual Solvents Guideline Q3R; Ph. Eur. General text 5.4. Residual Solvents; INFO 7.12/E; E.C. Safety Data Sheet
Residues of Metal Catalysts or Metal Reagents	Metal Catalysts or Metal Reagents are not used in the manufacture	CHMP Note for Guidance (CHMP/SWP/4446/2000)
Is heavy metal analysis performed?	Reduced Frequency Testing (RFT)	INFO 7.12/E RFT data available upon request
Lead	This Heavy metal is not used in the manufacture	See Heavy metals INFO 7.12/E

Question	Answer	Remarks / Further Information
Sodium Potassium Calcium Magnesium	Not more than 0.1 % each in the product	Calculated from the limit for Sulfated ash (max. 0.2 %)
Macronutrient information	N/A	The polymer is not absorbed and not degraded. It is excreted from the intestinal tract unchanged.
Allergen information	The allergens named in Directive 2003/15/EC, Directive 2007/68/EC and relevant amendments are not used in the manufacture of EUDRAGIT® FS 30 D.	Directive 2003/15/EC (Cosmetics) and relevant amendments Directive 2007/68/EC (Food Ingredients) and relevant amendments
e.g. Sulfur dioxide and Sulphites	Not expected to be more than 10 mg/kg	Analytical testing in preparation
Latex/-derivatives	No	
Does the product contain any of the following?		
Artificial colors	No	
Artificial flavors	No	
e.g. Vanillin	No	
Preservatives	No	
e.g. Formaldehyde	No	
Plasticizer	No	
e.g. Phtalates	No	
Emulsifiers	0.3 % Sodium Laurilsulfate 1.2 % Polysorbate 80 with reference to the dry substance	INFO 7.12/E
Simethicone	Minute amounts of a silicone antifoaming emulsion are used in the production process	Simethicone Emulsion USP
Antioxidants	No	
Pesticides	No	
Salt	No	
Amino Acids	No	
e.g. Glutamate	No	
L-Phenylalanine	No	

Question	Answer	Remarks / Further Information
Vegetable substances and derivatives	No	
e.g. Corn	No	
Wheat	No	
Soy	No	
Yeast	No	
Sugar	No	
Maltodextrin	No	
Sugar alcohol	No	
Starch	No	
Gluten	No	Commission Regulation (EC) No 1881/2006 (setting maximum levels for certain contaminants in foodstuffs) and relevant amendments
Aristolochic acid	No	
Latex/-derivatives	No	
Aflatoxin	N/A	
Animal derived substances and derivatives,	No	Neither animal nor human based materials are used in the manufacture of this product.
e.g. Bovine/chicken /pork derivatives	No	BSE/TSE Confirmation: See page 2 of the batch-related Certificate of Analysis
Dairy products/ derivatives	No	
e.g. Lactose	No	
Casein	No	
Collagen	No	
Animal Coal	No	
Wool derivatives	No	
Genetically modified material	No	Directive 2001/18/EC and relevant amendments For pharmaceuticals: EMEA/CHMP/BWP/473191/2006, For Food and Feed: Regulation (EC) No 1829/2003 and Regulation (EC) No 1830/2003
Conformance to Proposition 65		See E.C. Safety Data Sheet

EVONIK INDUSTRIES

Date:

2008-04-30

Dr. Thomas Brendel
Head of Quality Assurance
Pharma Polymers

Dr. Johanna Eisele
Head of Regulatory Affairs
Pharma Polymers

(written by computer and therefore not signed)

Encl.: Combined Certificate of DIN ISO 9001 and DIN ISO 14001
Environmental Protection, Safety, Health and Quality Policy EVONIK Röhm GmbH
Production Flow and Quality control of EUDRAGIT® L 30 D-55; EUDRAGIT® NE 30 D; EUDRAGIT® NE 40 D; EUDRAGIT® NM 30 D and EUDRAGIT® FS 30 D
Specification and Test Methods for EUDRAGIT® FS 30 D (INFO 7.12/E)

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Customer No.: 20462
Attorney Docket No. P51319
Confirmation No.: 8276

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	McAllister, et al.	17 September 2009	
Serial No.:	10/060,603	Group Art Unit No.:	1618
Filed:	30 January 2002	Examiner:	B. Fubara
For:	Pharmaceutical Formulation		

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT

Dear Sir:

In response to the Examiner's Action mailed 17 March 2009 having a shortened statutory period of three months, please enter the following Remarks and Amendments into the record.

EXTENSION OF TIME PETITION

Applicants hereby petition for a three (3) month extension of the shortened statutory period set by the Examiner, the fee being as follows:

( )	one month extension.....	$ 130
( )	two months extension.....	$ 490
(x)	three months extension.....	$1110
( )	four months extension.....	$1730

Please charge **$1,110.00** to Deposit Account No. 19-2570. Please charge any additional fees under 37 CFR 1.16 or 1.17 which may be required by this paper, or credit any overpayment, to Deposit Account No. 19-2570.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 17 of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of claims in the application:

1. (Previously presented) A capsule comprising a shell having an outer surface and an opposed inner surface, the inner surface defining at least in part a confined space for holding a drug substance, and the outer surface being exposed to a gastro-intestinal environment, the shell being composed of an extruded and injection molded capsule shell composition comprising:

Aminoalkyl Methacrylate Copolymer E present in an amount of 30 to 90% w/w,

a lubricant from [[0]] 10 to about [[30]] 25% w/w,

at least one dissolution modifying excipient which is polyethylene oxide present in an amount of about 5 to about 30% w/w; and optionally a second dissolution modifying excipient ~~present in an amount from about 5 to 70% w/w~~ selected from the ~~group consisting of~~

i) a swellable solid [,] selected from polyvinyl pyrrolidone, hydroxypropylmethyl cellulose, and other hydroxyalkylcellulose derivatives present in an amount from about 5% to about 60% w/w;

ii) a disintegrant [,]selected from sodium starch glycollate, croscarmellose sodium, cross-linked PVP, or copovidone present in an amount of about 5 to 50 % w/w;

iii) a non-reducing sugar [, and] selected from xylitol, or mannitol present in the amount of about 2.5 to 15% w/w;

iv) a water soluble filler [,] which is lactose present in the amount of about 5 to 20% w/w;

v) wicking agent selected from mannitol, lactose, or starch; present in the amount of about 2.5% to about 70% w/w; or

vi) an inorganic salt which is sodium chloride present in an amount of about 5 to about 10% w/w; or a combination or mixture thereof [,];

and optionally

a plasticizer from about 0 to 5% w/w and/or a processing agent from about 0 to about 10% w/w,

wherein the shell between and including the inner and outer surfaces is composed of the extruded and injection molded capsule shell composition.

2. (Previously presented) The capsule shell composition according to Claim 1 wherein the Aminoalkyl Methacrylate Copolymer E is present in an amount of 50 to 90% w/w.

3. (Previously presented) The capsule shell composition according to Claim 1 wherein the lubricant is stearyl alcohol, glycerol monostearate (GMS), talc, magnesium stearate, silicon dioxide, amorphous silicic acid, or fumed silica; and combinations or mixtures thereof.

4. (Previously presented) The capsule shell composition according to Claim 3 wherein the lubricant is stearyl alcohol.

5. (Previously presented) The capsule shell composition according to Claim 4 wherein the lubricant is present in an amount of about 5 to 15% w/w.

6. (Previously presented) The capsule shell composition according to Claim 5 the lubricant is stearyl alcohol and is present in an amount of about 10 to 12% w/w.

7. (Currently amended) The capsule shell composition according to Claim 1 wherein the second dissolution modifying excipient is [[poly(ethylene) oxide,]] ethyl cellulose, cellulose acetate phthalate, hydroxypropylmethyl cellulose (HPMC), hydroxypropylcellulose (HPC), lactose, Starch 1500, croscarmellose sodium, copovidone, or crospovidone (cross-linked polyvinyl pyrrolidone); and combinations or mixtures thereof.

8. (Currently amended) The capsule shell composition according to Claim 7 wherein the second dissolution modifying excipient is [[polyethylene oxide,]] lactose, HPMC, hydroxypropylcellulose (HPC), or copovidone; or combinations or mixtures thereof.

9. (Currently amended) The capsule shell composition according to Claim [[8]] 1 wherein the dissolution modifying agent is polyethylene oxide present in an amount of about 5 to 30% w/w.

10. (Previously presented) The capsule shell composition according to Claim 9 wherein the polyethylene oxide present in an amount of about 10 to 20 % w/w.

11. (Currently amended) The capsule shell composition according to Claim [[8 which]] 1 wherein the dissolution modifying excipient is a combination of polyethylene oxide, and at least one of lactose, HPMC, hydroxypropylcellulose (HPC), or copovidone.

12. (Previously presented) The capsule shell composition according to Claim 11 which is a combination of polyethylene oxide and copovidone.

13. (Previously presented) The capsule shell composition according to Claim 12 wherein the polyethyleneoxide is present in an amount of about 10 to 20% w/w, and the copovidone is present in an amount of 5 to 35% w/w.

14. (Withdrawn) The capsule shell composition according to Claim 1 wherein the plasticizer is triethyl citrate (TEC), tributyl citrate, acetyl triethyl citrate (ATEC), acetyl tributyl citrate (ATBC), dibutyl phthalate, dibutyl sebacate (DBS), diethyl phthalate, vinyl pyrrolidone glycol triacetate, polyethylene glycol, polyoxyethylene sorbitan monolaurate, propylene glycol, or castor oil; and combinations or mixtures thereof.

15. (Withdrawn) The capsule shell composition according to Claim 1 wherein the processing agent is talc.

16. (Withdrawn) The capsule shell composition according to Claim 15 wherein the talc is present in an amount of 5 to 10% w/w.

17. (Withdrawn) The capsule shell composition according to Claim 7 wherein the processing agent is talc present in an amount of 5 to 10% w/w, and the lubricant is stearyl alcohol present in an amount of 10 to 12% w/w.

18. (Withdrawn) The capsule shell composition according to Claim 1 which further comprises a surfactant.

19. (Withdrawn) The capsule shell composition according to Claim 18 wherein the surfactant is a block copolymers of ethylene oxide and propylene oxide, lecithin, sodium dioctyl sulfosuccinate, sodium lauryl sulfate, hydrogenated castor oil, polyoxyethylene sorbitan fatty acid esters, the sorbitan fatty acid esters, polyethylene glycol, glyceryl monostearate, d-alpha-tocopheryl polyethylene glycol 1000 succinate, sucrose fatty acid esters; and combinations and mixtures thereof.

20. (Withdrawn) The capsule shell composition according to Claim 19 wherein the surfactant is a block copolymer of ethylene oxide and propylene oxide.

21. (Withdrawn) The capsule shell composition according to Claim 19 or 20 wherein the surfactant is present in an amount of about 0.25 to 5% w/w.

22. (Withdrawn/amended) The capsule shell composition according to Claim 1 which is:

Example #	Formulation	% w/w

1	Aminoalkyl Methacrylate Copolymer E	75.0	
	Stearyl alcohol	5.0	
	Polyethylene oxide	20.0	or
2	Aminoalkyl Methacrylate Copolymer E	60.0	
	Hydroxypropyl cellulose	10.0	
	Polyethylene oxide	20.0	
	Stearyl alcohol	10.0	or
3	Aminoalkyl Methacrylate Copolymer E	60.0	
	Hydroxypropylmethyl cellulose	20.0	
	Polyethylene oxide	10.0	
	Stearyl alcohol	10.0	or
4	Aminoalkyl Methacrylate Copolymer E	60.0	
	Pregelatinized starch	20.0	
	Polyethylene oxide	10.0	
	Stearyl alcohol	10.0	or
~~5~~	~~Aminoalkyl Methacrylate Copolymer E~~	~~65.0~~	
	~~Glyceryl monostearate~~	~~5.0~~	
	~~Hydroxypropylmethyl cellulose~~	~~20.0~~	
	~~Stearyl alcohol~~	~~10.0~~	~~or~~
~~6~~	~~Aminoalkyl Methacrylate Copolymer E~~	~~65.0~~	
	~~Glyceryl monostearate~~	~~5.0~~	
	~~Pregelatinized starch~~	~~20.0~~	
	~~Stearyl alcohol~~	~~10.0~~	~~or~~
[[7]] 5	Aminoalkyl Methacrylate Copolymer E	55.0	
	Hydroxypropylmethyl cellulose	20.0	
	Polyethylene oxide	10.0	
	Lactose (regular)	5.0	
	Stearyl alcohol	10.0	or

[[8]] 6	Aminoalkyl Methacrylate Copolymer E	55.0	
	Hydroxypropylmethyl cellulose	15.0	
	Polyethylene oxide	10.0	
	Lactose (regular)	5.0	
	Starch 1500	5.0	
	Stearyl alcohol	10.0	or
[[9]] 7	Aminoalkyl Methacrylate Copolymer E	57.5	
	Hydroxypropylmethyl cellulose	15.0	
	Polyethylene oxide	10.0	
	Lactose (regular)	5.0	
	Pregelatinized starch	2.5	
	Stearyl alcohol	10.0	or
[[10]] 8	Aminoalkyl Methacrylate Copolymer E	70.0	
	Sucrose ester	10.0	
	Polyethylene oxide	10.0	
	Stearyl alcohol	10.0	.

23. (Currently amended) The capsule shell composition according to Claim 1 which is:

% w/w	Example 1 or	~~Example 2 or~~	Example [[3]] 2 or	Example [[4]] 3or	~~Example 5 or~~	~~Example 6 or~~	Example [[7]]4 or	~~Example 8 or~~	Example [[9]] 5 or
Aminoalkyl Methacrylate Copolymer E	75.0	~~55.0~~	70.0	62.5	~~67.5~~	~~80.0~~	30.0	~~45.0~~	42.5
Copovidone		~~35.0~~		17.5	~~17.5~~		35.0	~~35.0~~	17.5
Polyethylene oxide	10.0		20.0	10.0			20.0		20.0
Talc	5.0				~~5.0~~	~~10.0~~	5.0	~~10.0~~	10.0
Stearyl alcohol	10.0	~~10.0~~	10.0	10.0	~~10.0~~	~~10.0~~	10.0	~~10.0~~	10.0

	Example [[10]] 6 or	Example [[11]] 7 or	Example [[12]] 8 or	Example [[13]]9 or	Example [[14]] 10 or	Example [[15]] 11 or	Example [[16]] 12 or	Example [[17]] 13
Aminoalkyl Methacrylate Copolymer E	48.75	60.0	52.5	40.0	63.75	60.0	55.0	50.0
Copovidone	26.25		17.5	35.0	8.75	20.0	5.0	16.5
Polyethylene oxide	10.0	20.0	20.0	10.0	10.0	5.0	20.0	20.0
Talc	5.0	10.0		5.0	7.5	5.0	10.0	3.5
Stearyl alcohol	10.0	10.0	10.0	10.0	10.0	10.0	10.0	10.0

.

24. (Withdrawn/previously presented) The capsule shell composition according to Claim 1 which further comprises a second co-polymer which is Ammonio Methacrylate Copolymer Type A or Ammonio Methacrylate Copolymer Type B.

25. (Withdrawn/previously presented) The capsule shell composition according to Claim 24 which is:

Example #	Formulation	% w/w
1	Aminoalkyl Methacrylate Copolymer E	70.0
	Ammonio Methacrylate Copolymer Type A	20.0
	Stearyl alcohol	10.0

or

Example #	Formulation	% w/w
2	Aminoalkyl Methacrylate Copolymer E	60.0
	Ammonio Methacrylate Copolymer Type A	20.0
	Polyethyleneoxide	10.0
	Stearyl alcohol	10.0

.

26. (Previously presented) A capsule shell composition according to any one of Claims 1 to 20, 22 to 25 that is in the form of a molded capsule shell.

27. (Previously presented) A capsule shell composition according to any one of Claims 1 to 20, 22 to 25 that is in the form of a multicomponent injection molded capsule shell.

28. (Previously presented) A capsule shell composition according to any one of Claims 1 to 20, 22 to 25 that is in the form of a welded multicomponent injection molded capsule shell.

29 to 68 (cancelled).

69. (Withdrawn/Currently amended) A solid generally cylindrical linker body having an outer surface, the outer surface being exposed to a gastro-intestinal environment, the cylindrical linker body being composed of an extruded and injection molded pharmaceutical linker composition comprising

Aminoalkyl Methacrylate Copolymer E present in an amount of about 30 to about 90% w/w,

a lubricant from about 5 to about 30% w/w,

a first [[at least one]] dissolution modifying excipient which is polyethylene oxide present in an amount of about 5 to about 30% w/w; and optionally a second dissolution modifying excipient ~~present in an amount from about 5 to 70% w/w~~

i) a swellable solid [,] selected from polyvinyl pyrrolidone, hydroxypropylmethyl cellulose, and other hydroxyalkylcellulose derivatives present in an amount from about 5% to about 60% w/w;

ii) a disintegrant [,]selected from sodium starch glycollate, croscarmellose sodium cross-linked PVP, or copovidone present in an amount of about 5 to 50 % w/w;

iii) a non-reducing sugar [, and] selected from xylitol, or mannitol present in the amount of about 2.5 to 15% w/w;

iv) a water soluble filler [,] which is lactose present in the amount of about 5 to 20% w/w;

and

optionally a plasticizer from about 0 to about 5% w/w and/or a processing agent from about 0 to about 10% w/w,

wherein the cylindrical linker body is comprised of the extruded and injection molded linker composition.

70. (Withdrawn) The linker composition according to Claim 69 wherein the lubricant is stearyl alcohol, or talc or a combination thereof.

71. (Withdrawn) The linker composition according to Claim 70 wherein the lubricant is present in an amount of about 5 to about 15% w/w.

72. (Withdrawn) The linker composition according to Claim 70 wherein the lubricant is present in an amount of about 10 to about 15% w/w.

73. (Withdrawn) The linker composition according to Claim 70 wherein the lubricant is present in an amount of about 10 to about 25% w/w.

74. (Withdrawn) The linker composition according to Claim 70 wherein the lubricant is stearyl alcohol present in an amount of about 10 to about 15% w/w.

75. (Withdrawn) The linker composition according to Claim 69 wherein the dissolution modifying excipient is a swellable solid.

76. (Withdrawn/currently amended) The linker composition according to Claim 75 wherein the swellable solid is [[polyethylene oxide,]] hydroxypropylcellulose (HPC), or hydroxypropylmethylcellulose (HPMC); or a combination thereof.

77. (Withdrawn/currently amended) The linker composition according to Claim [[76]] 69 wherein the ~~dissolution modifying agent is~~ polyethylene oxide is present in an amount of about 5 to about 30% w/w.

78. (Withdrawn/currently amended) The linker composition according to Claim [[76]] 69 wherein the polyethylene oxide present in an amount of about 10 to 20 % w/w.

79. (Withdrawn/currently amended) The linker composition according to Claim [[75]] 69 ~~which further comprises a~~ wherein the second dissolution modifying excipient [[which]] is a disintegrant.

80. (Withdrawn) The linker composition according to Claim 79 wherein the disintegrant is crospovidone (cross-linked polyvinyl pyrrolidone), or copovidone, or a combination thereof.

81. (Withdrawn) The linker composition according to claim 79 wherein the disintegrant is presenting the range of about 5 to about 50 % w/w.

82. (Withdrawn) The linker composition according to claim 79 wherein the disintegrant is present in the range of about 10 to about 40%.

83. (Withdrawn/currently amended) The linker composition according to Claim [[75]] 69 ~~which further comprises a~~ wherein the second dissolution modifying excipient [[which]] is a non-reducing sugar, or a water soluble filler.

84. (Withdrawn) The linker composition according to Claim 83 wherein the non-reducing sugar is xylitol, or mannitol.

85. (Withdrawn) The linker composition according to Claim 83 wherein the non-reducing sugar is present in the range of about 2.5 to about 15% w/w.

86. (Withdrawn) The linker composition according to Claim 83 wherein the non-reducing sugar is present in the range from about 5 to about 10% w/w.

87. (Withdrawn) The linker composition according to Claim 83 wherein the water soluble filler is lactose.

88. (Withdrawn) The linker composition according to Claim 83 wherein the water soluble filler is present in the range of about 5 to about 20% w/w.

89. (Withdrawn) The linker composition according to Claim 83 wherein the water soluble filler is present in the range of about 5 to about 10% w/w.

90. (Withdrawn/currently amended) The linker composition according to Claim [[75]] 69 ~~which further comprises a~~ wherein the second dissolution modifying excipient [[which]] is a disintegrant, and optionally a third dissolution modifying excipient which is a non-reducing sugar, or a fourth dissolution modifying excipient which is a water soluble filler~~.~~

91. (Withdrawn) The linker composition according to Claim 90 wherein the disintegrant is crospovidone (cross-linked polyvinyl pyrrolidone), or copovidone, or a combination thereof.

92. (Withdrawn) The linker composition according to Claim 90 wherein the non-reducing sugar is xylitol, or mannitol, and the water soluble filler is lactose.

93. (Withdrawn) The linker composition according to Claim 90 which is a combination of polyethylene oxide, and at least one of lactose, HPMC, hydroxypropylcellulose (HPC), or copovidone.

94. (Withdrawn) The linker composition according to Claim 69 wherein the processing agent is talc.

95. (Withdrawn) The linker composition according to Claim 94 wherein the talc is present in an amount of about 5 to about 10% w/w.

96. (Withdrawn) The linker according to Claim 69 wherein the processing agent is talc present in an amount of 5 to about 10% w/w, and the lubricant is stearyl alcohol present in an amount of about 10 to about 12% w/w.

Claims 97-102 (Cancelled)
Claims 103 and 104. (Cancelled)

105. (Withdrawn/previously presented) The linker composition according to Claim 70 wherein the stearyl alcohol is material is suitable for milling.

106. (Withdrawn/previously presented) The linker composition according to Claim 97 wherein the stearyl alcohol is material is suitable for milling.

107. (Cancelled)

108. (Currently amended) The capsule shell composition according to Claim 1 wherein the second dissolution modifying excipient is a swellable solid selected from [[poly(ethylene) oxide,]] hydroxypropyl cellulose (HPC), or hydroxypropylmethyl cellulose (HPMC), or a combination thereof, and wherein the swellable solid is present in an amount of about 5% to about 60% w/w.

109. (Currently amended) The capsule shell composition according to Claim 1 wherein the second dissolution modifying excipient is a disintegrant selected from sodium starch glycollate, crospovidone or copovidone, present in an [[about]] amount of about 5% to 50% w/w.

110. (Currently amended) The capsule shell composition according to Claim 1 wherein the second dissolution modifying excipient is a swellable solid, the lubricant is stearyl alcohol, and optionally contains a plasticizer and/or a processing aid.

111. (Previously presented) The capsule shell composition according to Claim 1 wherein the wall thickness is in the range of about 0.3 – 0.8 mm.

112. (Withdrawn) The linker composition according to claim 80 wherein the disintegrant is present in the range of about 5 to about 50 % w/w.

113. (Withdrawn) The linker composition according to claim 80 wherein the disintegrant is present in the range of about 10 to about 40%.

114. (Withdrawn/currently amended) The linker composition according to Claim 83 wherein the [[first]] second dissolution modifying excipient is a swellable solid.

115. (Withdrawn/currently amended) The linker composition according to Claim 114 wherein the swellable solid is [[polyethylene oxide,]] hydroxypropylcellulose (HPC), or hydroxypropylmethylcellulose (HPMC); or a combination thereof.

116. (Cancelled)

117. (Currently amended) The capsule shell composition according to claim 1 wherein the second ~~at least one~~ dissolution modifying excipient is a non-reducing sugar present in the range of about 2.5 to 15% w/w, or is a water soluble filler present in the range of about 5 to 20% w/w.

118. (Cancelled)

119. (Currently amended) The capsule shell composition according to Claim 1 which comprises a [[first]] second dissolution modifying excipient which is a disintegrant, and optionally a [[second]] third dissolution modifying excipient which is a non-reducing sugar, ~~and optionally a third dissolution modifying excipient which is~~ a water soluble filler.

120. (Previously presented) The capsule shell composition according to Claim 119 wherein the disintegrant is crospovidone (cross-linked polyvinyl pyrrolidone), or copovidone, or a mixture thereof.

121. (Withdrawn/currently amended) The capsule shell composition according to Claim 1 wherein the at least one dissolution modifying excipient is [[a swellable solid]] polyethylene oxide, and [[further comprises a]] the second dissolution dissolution modifying excipient ~~which~~ is a disintegrant.

122. -123. (Cancelled)

124. (Withdrawn/Previously presented) A capsule comprising a shell having an outer surface and an opposed inner surface, the inner surface defining at least in part a confined space for holding a drug substance, and the outer surface being exposed to a gastro-intestinal environment, the shell being composed of an extruded and injection molded capsule shell composition comprising Aminoalkyl Methacrylate Copolymer E present in an amount of about 55% w/w, stearyl alcohol present in an amount of about 10% w/w, copovidone present in an amount of about 5%, polyethylene oxide present in an amount of about 20% w/w and talc present in an amount of about 10% w/w, wherein the shell between and including the inner and outer surfaces is composed of the extruded and injection molded capsule shell composition.

125. (Withdrawn/ Previously presented) A capsule comprising a shell having an outer surface and an opposed inner surface, the inner surface defining at least in part a confined space for holding a drug substance, and the outer surface being exposed to a gastro-intestinal environment, the shell being composed of an extruded and injection molded capsule shell composition comprising Aminoalkyl Methacrylate Copolymer E present in an amount of about 60% w/w, stearyl alcohol present in an amount of about 10% w/w, polyethylene oxide present in an amount of about 20% w/w and talc present in an amount of about 10% w/w, wherein the shell material between and including the inner and outer surfaces is composed of the extruded and injection molded capsule shell composition.

126. (Previously presented) A capsule comprising a shell having an outer surface and an opposed inner surface, the inner surface defining at least in part a confined space for holding a drug substance, and the outer surface being exposed to a gastro-intestinal environment, the shell being composed of an extruded and injection molded capsule shell composition comprising Aminoalkyl Methacrylate Copolymer E present in an amount of about 30 to 60% w/w, stearyl alcohol present in an amount from about 10 to 12% w/w, polyethylene oxide present in an amount of about 10 to 20% w/w, present in an amount of about talc from about 0 to 10% w/w, and copovidone present in an amount of about 0 to 35 % w/w.

Remarks:

Claims 1-28, 69-96, 105, 106, and 108-115, 117, 119-121, and 124-126 are in the present application. Claims 97-102, 116, 118, 122 and 123 have been cancelled. Claims 1, 7-9, 11, 22, 23, 69, 76-79, 83, 90, 108-110, 114, 115, 117, 119, 121 have been amended. Support for the amendments lie in the working examples, and in the specification on page 27, line 37, page 28, lines 1 to 15, lines 27-29, lines 36-37, page 29, lines 1-9. Applicants reserve their right to file divisional or continuation applications on all cancelled or deleted subject matter. Claims 1-13, 23, 26-28,108-111, 117-120 and 126 are noted as being examined.

Applicants believe that this is an improper final rejection and respectfully request that it be withdrawn. The Examiner has given a new rejection to the claims over two secondary references that have never bee cited previously. The subject matter of the claims has not changed substantially to warrant an undue burden on the Examiner, and as such, a final office action places the Applicants in an unfair position for arguments to be adequately addressed in response to the newly cited art.

Applicants also respectfully request that the IDS and 1449 form recently submitted be entered into the record in this application as the finality of the rejections herein are improper.

I. Rejection of Claims Based on Non-Statutory Obviousness-Type Double Patenting

The Examiner has maintained the provisional rejection of claims 1-13, 23, 26-28, 108-111, 117-120 and 126 on the ground of non-statutory obviousness-type double patenting over claims 29, 31-45, 47-61 and 69-128 of Applicant's copending Application No. 10/470,439. Applicants respectfully traverse this rejection.

As previously noted in Applicants response of December 5, 2008 the claims in this application were made the subject of a restriction requirement on 23 April 2003 between the multicomponent dosage forms and the singular components as presently claimed herein, which Applicant did not traverse. The multicomponent dosage form claims always contained the subject matter of the individual components, e.g. the linker and the individual

capsule shell. The point of the multicomponent claim is that only one of these individual components having being composed of the formulations as claimed therein was required.

The Examiner's comments are that:

> "the restriction and election of April 23, 2003 is not the current restriction. Co-pending claim 29 (filed 11/13/2008) is directed to a capsule shell that has the outer and inner……; and in the manner, the capsule composition of the examined claim 1 comprising aminoalkyl methacrylate copolymer E, lubricant and optional plasticizer would intrinsically dissolve being capable of dissolving in the gastro-intestinal environment of a patent. The rejection is therefore proper".

The Examiner's arguments are not articulated in a clear and concise manner, but Applicants believe that the rejection is based upon the fact that the composition of the capsule shell in the multicomponent dosage form is the same or similar to that as the one here claimed herein.

Applicants have never disputed that these two inventions were intertwined, but it was the USPTO that made the initial restriction. Because of this restriction, and reliance thereon the invention was lawfully divided out. Therefore, the subject matter of those claims were not presently in the instant application for the Examiner to make a second restriction. This does not change the fact that Applicants are entitled to rely upon the USPTO's original restriction in this application. The claims of co-pending application USSN 10/470,439 are directed to the subject matter of some of the non-elected group(s) from the original restriction. It is therefore, improper, for a rejection to be made in this application on the grounds of non-statutory obviousness-type double patenting. In view of the prior restriction and subsequent lawful reliance upon it, withdrawal of the obviousness-type double patenting is respectfully requested.

In view of these remarks, reconsideration and withdrawal of the rejection to the claims under the Doctrine of Obviousness -type double patenting is respectfully requested.

II. Rejection of Claims Under 35 U.S.C. §103(a)

The Examiner has maintained the rejection to Claims 1-13, 23, 26-28, 108-111, 117-120 and 126 as being unpatentable under 35 U.S.C. §103(a) over Hatano (US 6,309,666, hereinafter '666) in view of Hay (US 3,723,312, hereinafter '312) and Grief et al. (US 3,394,983, hereinafter '983). The Applicants respectfully traverse these rejections.

The specification teaches it is possible to have differing release rates of the contents of the capsule shell, and differing rates of release of the linker from the capsule subunits. These differing release rates are determined by polymeric composition that the capsule shells and subunits are composed of. The primary polymer along with the amounts of and types of excipients added to the polymer determine whether the release will be immediate or delayed. This is described throughout the specification and in particular on pages 30 and 31. These releases are also categorized in the specification on page 36 as "Fast Release/Pulse Capsules or Components", and on page 35 as "Slow/delayed Release/Pulse Capsules or Components". The polymeric composition of the present application, which is extruded and injection molded into the capsule shells or the linker subunits as claimed herein is a fast release component.

As noted above, the present invention is directed to a capsule shell which has the characteristics of immediate release of the contents upon entry into the gastric fluids, as opposed to systems which are directed to release in the small intestines, or in the colon.

It is not a simple matter to formulate a polymeric coating material, such as E100, to become an extruded and injection molded article of manufacture. The same excipients, if even present in the material used for coating tablets, etc., are not necessarily present in the same amounts for extrusion and injection molding. Too much lubricant in the formulations and the shells become to flexible and can not be clipped or welded together. Too little plasticizer and the shells can become brittle and crack. Nothing in the prior art provide the basis for the formulation as claimed, nor the processing /manufacturing steps as described herein.

The dissolution modifying excipient (DME) as used in the instant invention was previously examined as at least one DME which was selected from a swellable solid, a disintegrant, a non-reducing sugar, or a water soluble filler, or a combination or mixture thereof.

In order to advance prosecution and more distinctly claim the invention, Applicants have further amended the claims to require the primary dissolution modifying excipient to be a specific swellable solid which is poly(ethylene)oxide. The formulation may comprise an optional second, or third, etc. DME which is selected from other swellable solids, disintegrants, non-reducing sugars, low molecular weight solutes, water soluble fillers, and a combination or mixture thereof.

Claim 1 has also been amended to also recite a narrower amount of lubricant, as supported in the specification on page 28, as from "about 10 to about 25% w/w".

The Examiner cites Hatano as describing "hard capsules that comprises binders, disintegrants and lubricants." (See Office Action, page 6, 2nd line, 3rd full ¶). The Examiner also states that the hard capsule comprising the enteric coating film…. meets the limitation of claims 1 and 126 except for the amount of the copolymer, Eudragit E100."

It is unclear to Applicants how the Hatano '666 disclosure can meet all the limitation of Claim 1 and 126.

Claim 1 is shown below. The preamble requires the capsule shell to be composed of "an extruded and injection molded composition comprising..." The body of the claim also recites a similar requirement of "herein the shell between and including the inner and outer surfaces is composed of the extruded and injection molded capsule shell composition."

> A capsule comprising a shell having an outer surface and an opposed inner surface, the inner surface defining at least in part a confined space for holding a drug substance, and the outer surface being exposed to a gastro-intestinal environment,

the shell being composed of an extruded and injection molded capsule shell composition comprising:

Aminoalkyl Methacrylate Copolymer E present in an amount of 30 to 90% w/w,

a lubricant from 10 to about 25% w/w,

at least one dissolution modifying excipient which is polyethylene oxide present in an amount of about 5 to about 30% w/w; and optionally a second dissolution modifying excipient selected from the

i) a swellable solid selected from polyvinyl pyrrolidone, hydroxypropylmethyl cellulose, and other hydroxyalkylcellulose derivatives present in an amount from about 5% to about 60% w/w;

ii) a disintegrant selected from sodium starch glycollate, croscarmellose sodium, cross-linked PVP, or copovidone present in an amount of about 5 to 50 % w/w;

iii) a non-reducing sugar selected from xylitol, or mannitol present in the amount of about 2.5 to 15% w/w;

iv) a water soluble filler which is lactose present in the amount of about 5 to 20% w/w;

v) wicking agent selected from mannitol, lactose, or starch; present in the amount of about 2.5% to about 70% w/w; or

vi) an inorganic salt which is sodium chloride present in an amount of about 5 to about 10% w/w; or a combination or mixture thereof,

and optionally

a plasticizer from about 0 to 5% w/w and/or a processing agent from about 0 to about 10% w/w,

wherein the shell between and including the inner and outer surfaces is composed of the extruded and injection molded capsule shell composition.

The Hatano '666 reference does not teach, does not suggest, nor does it describe a capsule that can be extruded and injection molded regardless of the resulting composition of the shell.

Consequently, the Hatano reference fails to meet even the most basic requirements of the invention as claimed herein.

Not withstanding the most basic of the limitations noted above, the Hatano '666 reference does not teach nor suggest

a) E100 to be present in the composition that the shell is composed of in the 30-90% w/w range;

b) a lubricant present in the composition that the shell is composed of in the 10 to 25% w/w range;

c) polyethylene oxide present in the composition that the shell is composed of in the 5 to 30% w/w range.

Dependent Claim 7 further requires a second dissolution modifying excipient which is selected from ethyl cellulose, cellulose acetate phthalate, hydroxypropylmethyl cellulose (HPMC), hydroxypropylcellulose (HPC), lactose, Starch 1500, croscarmellose sodium, copovidone, or crospovidone (cross-linked polyvinyl pyrrolidone); and combinations or mixtures thereof.

Not withstanding the most basic of the limitations noted above, the Hatano '666 reference does not teach nor suggest a second excipient in combination with polyethylene oxide.

Claim 108 is a specific second dissolution modifying excipient, a swellable solid. The Hatano '66 reference does not teach nor suggest a second excipient in combination with polyethylene oxide which is a swellable solid composition that the shell is composed of in the 5% - 60% w/w.

The Hatano, '666 patent does not teach inclusion of poly(ethylene)oxide in their coating materials.

Consequently, Hatano '6666 fails to meet the most basic limitations as claimed in Claim 1.

There is a significant difference between uses of an acrylic copolymer composition for film-coating a capsule shell and the use of the acrylic copolymer composition to make a capsule shell. The physical characteristics of these two distinct capsules are significantly different as well. The former is a multi-layer construct of film-coatings on a capsule shell, e.g. that disclosed by Hatano et al., wherein the enteric coating and the inner layer coating provide for certain (e.g. delayed) release characteristics of the final dosage form. The latter is a single – layer structure providing for, (in this instance) immediate release characteristics.

The Hatano pulse release dosage form performance:

1) It is an enteric layer (acrylic copolymer) that dissolves when the unit enters the small intestine and is exposed to pH>5.5;

2) The coated inner layer of E100 polymer on the capsule shell swells and hydrates but does not dissolve;

3) Fluid enters the capsule body (dissolving the gelatin or the HPMC capsule wall) at a rate determined by the thickness of the E100 coating and then begins to dissolve the acidic capsule contents;

4) Dissolution of the E100 layer is controlled by the amount and/or type of acid contained within the capsule fill and the thickness of the E100 coating;

5) The assembly of discrete layers is the essence of the Hatano claims.

In contrast the capsule shell (and the linker subunits) are physically made from the claimed formulation, in contrast to the disclosure of Hatano et al in which a capsule shell is coated with cellulosic derivatives and acrylic copolymers such as Eudragit S or E100.

Hatano et al. fails to provide any motivation to direct the skilled artisan to pick and choose a thermoplastic polymer, and various additives necessary to be incorporated within the chosen polymer in order to make a pharmaceutically acceptable formulation which is used in the manner disclosed herein, e.g. to become the composition which actually comprises the capsule shell wall as opposed to being overcoated on the capsule shell itself. The end use or outcome of the teachings of Hatano is completely different than that used herein. Hatano et al. directs

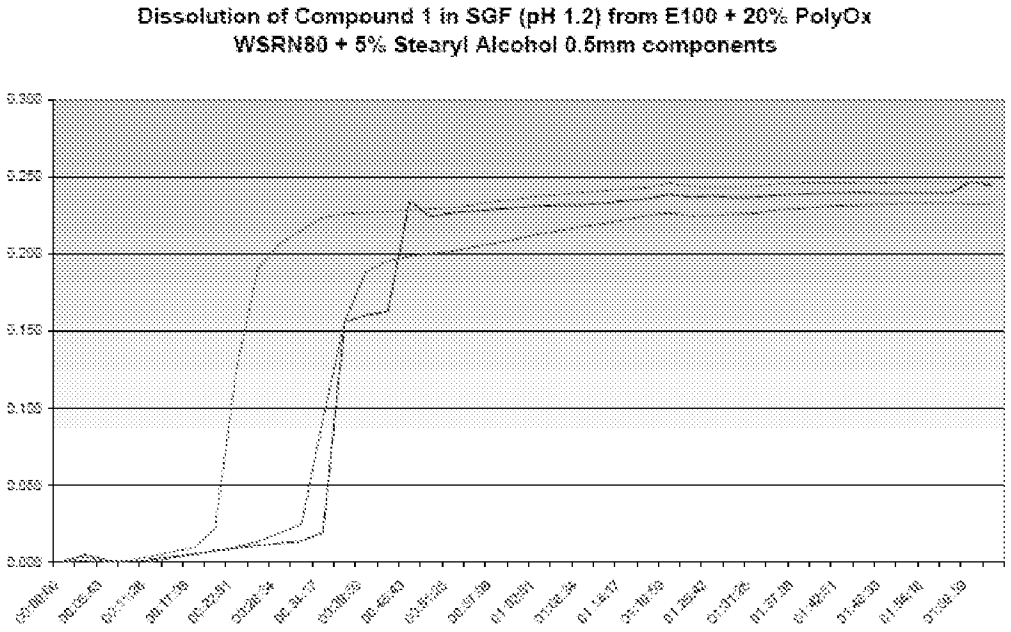
the skilled artisan towards problems associated with the coating arts in contrast to the present invention which is directed towards and immediate release injection molded article.

Claim 1, as amended, requires the capsule shell to be a molded article composes of E100 in an amount of about 30-90% w/w and specifically requires polyethyleneoxide to be present in that molded article in an amount of about 5-30 %w/w, along with a lubricant in the about of about 10-25% w/w.

There is nothing in the disclosure of Hatano et al. that the skilled artisan would look to in order to produce injection molded components having these particular characteristics as claimed herein. It is unclear what Hatano et al. contributes to direct the skilled artisan to use those teachings in combination with the teachings of the Hay or Grief et al. patents. Hatano et al. does not teach nor suggest that a *cationic* methacrylate copolymer will result in a thermostable, processable E100 capsule part or component. Hatano et al. simply describes using the Eudragit E100 as an overcoating, applied in the traditional manner. The fact that the E100 is combined with additional discrete layers and a particular capsule fill is irrelevant to the point at hand. The E100 is not taught to be in a composition which becomes an integral part of the capsule shell wall.

More importantly the device disclosed in Hatano is ultimately one which delivers the shell contents in a controlled, and delayed release manner. In contrast, Applicants capsules dissolves within a 17 to 34 minute window, immediately delivering the drug to the stomach contents, not as a controlled release mechanism over a 10 hour period, from 2 to 12 hours.

See Figure 2 below:



Consequently, for all the reasons noted above the Hatano '666 patent does not teach or suggest all the limitations of claim 1.

The secondary reference of Hay et al. '312 is directed to a method for packaging glass sheets. The glass is protected from staining and mechanical surface damage by and active stain retardant. The stain retardant is a solid organic acid, preferably salicylic acid or benzoic acid, made by mixing with the acid with a binder. The binder may be polyethylene oxide. It is unclear from the Examiner's comments how PEO used in combination with an organic acid as a stain inhibiting agent would be useful as a particular swellable solid in an extruded and injection molded object.

As Hatano et al., does not teach nor suggest use of binders and lubricants in the composition of the extruded and injection molded shell, the suggestion that a 'binder' would be useful in the formulations of Hatano, as indicated by the Examiner would be an impermissible hindsight rejection based upon the Applicants own specification. There needs to be a suggestion or motivation in the primary reference to direct the skilled artisan to look

elsewhere for such as teaching. Hatano fails to teach the required limitations of claim 1. The use of the secondary reference of Hay et al. also fails to remedy the missing limitations.

The other secondary reference of Grief et al. ('983) is directed to immersion dyeing of gelatin capsule shells, both hard and soft. The dye solution is preferably a lower alkanol water solution. The capsule shells may be dusted with stearyl alcohol to keep them from sticking to each other (column 2, lines 5-6). However, if they are dusted then they are rinsed in solvent prior to dying. (column 2, lines 7-9).

The Examiner comments that:

> "Grief discloses that hard capsule shell can comprise stearyl alcohol lubricant and the mixture of polyethylene oxide and polyvinylpyrrolidone-vinylacetate copolymers and the stearyl alcohol meets the claims 4, 7-13, 23, 108-110 and 126". See Office Action, page 7, middle of first ¶)

The Examiner has failed to point out with particularity where in the Grief reference tit teaches that hard capsule shells are comprised of "stearyl alcohol lubricant", and where they are comprised of "the mixture of polyethylene oxide and polyvinylpyrrolidone-vinylacetate copolymers".

Applicants can only find within the patent the above disclosure that the shells may be dusted with stearyl alcohol in column 2, lines 5-9. No where does the patent indicate that HARD capsule shells were a) comprised of stearyl alcohol, nor that b) HARD shells were actually dusted with stearyl alcohol.

Looking at Example 2 of the '983 the capsules were washed to remove stearyl alcohol prior to dipping. The capsules in Example 2 were made as in Example 1. The capsules used in Example 1 are soft gelatin <u>not</u> hard gelatin shells.

Further no where within the Grief '983 patent are the words "mixture of polyethylene oxide and polyvinylpyrrolidone-vinylacetate copolymers" ever used. Example 8 uses a surfactant

which is polyoxyethylene sorbitan monolaurate (Tween 20). Clarification of this aspect of the rejection is respectfully requested.

Notwithstanding the fact that the basis for use of the Grief patent by the Examiner appears to be for the use of Stearyl alcohol, the stearyl alcohol is not incorporated into the shell of the capsule. The stearyl alcohol is not even used in the dyeing solution that the capsule shell picks up. The stearyl alcohol is washed off prior to the dyeing even occurring. Consequently, it is unclear how the Examiner is making the necessary argument that one skilled in the art would be motivated to use the teachings of Grief et al. and incorporate those teachings into the disclosure of Hatano and achieve Applicants claimed invention herein.

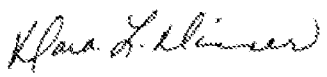
For all the reasons of record, the Examiner is respectfully requested to withdraw the rejection of these claims under 35 U.S.C. §103(a) and to issue a Notice of Allowance.

Applicants also enclose herewith their last response in copending application 10/470,439.

CONCLUSION

Should the Examiner have any questions or wish to discuss any aspect of this application, the Examiner is encouraged to call the undersigned attorney at the number below. If any additional fees or charges are required by this paper the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,



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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Mc Allister et al.
Serial No.: 10/470,439
Filed: 20 January 2004
For: PHARMACEUTICAL FORMULATION

17 March 2009
Group Art Unit No.: 1618
Examiner: J. W. Rogers

Commissioner for Patents
P.O. Box 1450
Arlington, VA 22313-1450

RESTRICTION & AMENDMENT

Sir:

Applicants now respond to the Office Action of 17 February 2009 for which entry of the following Remarks and Amendments into the record is respectfully requested.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 17 of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of the claims in the application:

1 to 28 (Cancelled).

29. (Withdrawn) A multi-component pharmaceutical dosage form which comprises at least two sub-units, each sub-unit being selected from:

a) an extruded and injection molded capsule shell having an outer surface and an opposed inner surface, the shell comprising a blend of:

aminoalkyl methacrylate copolymer E present in an amount of about 50 to 90% w/w;

a lubricant from about 0 to about 30% w/w;

at least one dissolution-modifying excipient present in an amount from about 5 to 70% w/w and being selected from the group consisting of a swellable solid, a disintegrant, a non-reducing sugar, a water soluble filler, and a combination or mixture thereof; and

optionally a plasticizer from about 0 to 5% w/w and/or a processing agent from about 0 to 10% w/w;

the inner surface of the shell defining, at least in part, a confined space for containing a drug substance;

wherein the shell is soluble or disintegrable in a patient's gastro-intestinal environment for release of the drug substance contained in the shell;

and at least one of:

b) a solid matrix being comprised of a polymeric composition comprising a drug substance, the polymeric composition being soluble, dispersible or disintegrable in a patient's

gastro-intestinal environment for release of the drug substance contained in the solid matrix; or

c) a solid generally cylindrical linker body having an outer surface, the outer surface being exposed to the patient's gastro-intestinal environment, the cylindrical linker body being composed of an extruded material comprising a pharmaceutical composition which is soluble, dispersible or disintegrable in the patient's gastro-intestinal environment;

and in which, at least prior to administration to a patient, the at least two sub-units are assembled together into a dosage form.

30.(cancelled)

31. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29, in which the lubricant is present in an amount up to about 15% w/w.

32. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 31, in which the lubricant is stearyl alcohol and/or glyceryl monostearate.

33. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29, in which the lubricant is selected from the group consisting of stearyl alcohol, glycerol monostearate (GMS), talc, magnesium stearate, silicon dioxide, amorphous silicic acid, and fumed silica; and combinations or mixtures thereof.

34. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29 in which the processing agent is talc.

35. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29, in which the dissolution-modifying excipient of the shell is polyethylene oxide.

36. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29, in which the dissolution-modifying excipient of the shell is a combination of polyethyleneoxide, talc, Starch 1500, lactose, hydroxypropylmethyl-cellulose, or co-povidone.

37. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 36, in which the lubricant is stearyl alcohol.

38. (Withdrawn) A dosage form according to Claim 29, comprising a plurality of drug substance-containing sub-units, wherein at least one sub-unit comprises the extruded and injection molded shell made of a pharmaceutically acceptable polymeric composition comprising Aminoalkyl Methacrylate Copolymer E present in an amount of about 50 to 90% w/w, and a dissolution-modifying excipient present in an amount of about 10 to about 30% w/w; and at least one of the solid matrix sub-unit or the linker body sub-unit is composed of polymeric composition comprising a copolymer of methacrylic acid, methyl acrylate and methyl methacrylate with a molar ratio of the monomer units of 7:3:1.

39. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 38, in which the Aminoalkyl Methacrylate Copolymer E is present in an amount of about 30 to 90% w/w, and-the lubricant is selected from the group consisting of stearyl alcohol, glycerol monostearate (GMS), talc, magnesium stearate, silicon dioxide, amorphous silicic acid, and fumed silica; and combinations or mixtures thereof.

40. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 39, in which the lubricant is present in an amount up to about 15% w/w.

41. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 39, in which the lubricant is present in an amount of about 5 to 15% w/w.

42. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 39, in which the polymeric composition further comprises a processing agent present in an amount up to about 10% w/w.

43. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29, in which at least one of the sub-units is a drug substance-containing capsule compartment

having a wall with a thickness in the range of about 0.3 – 0.8 mm.

44. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29, in which at least one of the sub-units releases the drug substance as a substantially immediate release.

45. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29, in which at least one of the sub-units releases the drug substance as a sustained release or pulsed release.

46.(cancelled)

47. (Previously presented) A process for making a pharmaceutical dosage form comprising the steps of:

a) introducing Aminoalkyl Methacrylate Copolymer E present in an amount of about 50 to 90% w/w and an excipient composition comprising at least one dissolution-modifying excipient present in an amount from about 5 to 70% w/w selected from the group consisting of a swellable solid, a disintegrant, a non-reducing sugar, and a water soluble filler, and combinations or mixtures thereof, and a lubricant present in an amount up to about 15% w/w, simultaneously into a first location of an elongated hot melt extruder, the first location having a temperature of about 50°C;

b) mixing said Aminoalkyl Methacrylate Copolymer E and said excipient composition in the hot melt extruder at a temperature ranging from about 50°C to about 125°C to form a homogeneous composition therein and substantially without thermal degradation of the Aminoalkyl Methacrylate Copolymer E and the excipient composition;

(c) extruding the homogeneous composition in the form of a strand from the hot melt extruder though a die at a second location distal from said first location, said second location having a temperature not greater than about 125°C;

c) cutting the strand into pellets; and

d) introducing said pellets into an injection molder and forming thin-walled capsule compartments from said pellets by injection molding.

48. (Previously presented) The process according to Claim 47, wherein the dissolution modifying excipient is poly(ethylene) oxide, ethyl cellulose, cellulose acetate phthalate, hydroxypropylmethyl cellulose (HPMC), lactose, Starch 1500, croscarmellose sodium, copovidone, or crospovidone (cross-linked polyvinyl pyrrolidone); or combinations or mixtures thereof.

49. (Previously presented) The process according to Claim 48, wherein the dissolution modifying excipient is polyethylene oxide.

50. (Previously presented) The process according to Claim 47 wherein the lubricant is stearyl alcohol, glycerol monostearate (GMS), talc, magnesium stearate, silicon dioxide, amorphous silicic acid, or fumed silica; or combinations or mixtures thereof.

51. (Previously presented) The process according to Claim 47, in which the hot melt extruder is maintained at a temperature not exceeding approximately 120°C.

52. (previously presented) The process according to Claim 47, in which the hot melt extruder is maintained at a temperature not lower than the Aminoalkyl Methacrylate Copolymer E and said excipient composition melting points.

53. (Previously presented) The process according to Claim 47, in which the temperature in the hot melt extruder gradually increases along the length of the hot melt extruder, from said first location at which the Aminoalkyl Methacrylate Copolymer E and an excipient composition are introduced, to the die, the maximum temperature not exceeding approximately 125°C.

54. (Previously presented) The process according to Claim 47, in which the hot melt extruder comprises an elongated barrel having first and second opposite ends, and twin screws within the barrel for propelling Aminoalkyl Methacrylate Copolymer E and said excipient composition along the length of the interior of the barrel, said first location at which the

Aminoalkyl Methacrylate Copolymer E and said excipient composition are introduced being located adjacent the first end of the barrel, and said die being located adjacent the second end of the barrel.

55. (Previously presented) The process according to Claim 47, in which the injection molding of the thin-walled capsule compartments is carried out using an injection molder having a barrel and a nozzle, while maintaining the injection molder barrel at a temperature in the range of about 110°C to 130°C.

56. (Previously presented) The process according to Claim 47, in which the injection molding of the thin-walled capsule compartments is carried out using an injection molder having a barrel and a nozzle, while maintaining the injection molder nozzle at a temperature in the range of about 130°C to 150°C.

57. (Previously presented) The process according to Claim 47, in which the injection molding of the thin-walled capsule compartments is carried out using an injection molder having a barrel and a nozzle, while maintaining the injection molder nozzle at a temperature of about 140°C.

58. (Previously presented) The process according to Claim 47, in which the injection molding of the thin-walled capsule compartments is carried out using an injection molder having a barrel and a nozzle, while maintaining the injection molder barrel at a temperature in the range of about 110°C to 130°C and maintaining the injection molder nozzle at a temperature in the range of about 130°C to 150°C.

59. (original) The process according to Claim 47 wherein the pharmaceutical dosage forms are assembled using said capsule compartments as components of said dosage forms.

60. (original) The process according to Claim 59 wherein the said capsule compartments of the assembled dosage form are connected together by at least one weld where adjacent parts of said components are in contact.

61. (original) The process according to Claim 60 wherein the weld is produced by a thermal weld, an ultrasonic weld, an inductive weld, or an adhesive weld.

62 – 68 (cancelled).

69. (Previously presented) A method for making an extruded pharmaceutically acceptable composition comprising:

a) mixing Aminoalkyl Methacrylate Copolymer E present in an amount of about 30 to 90% w/w; a lubricant from about 0 to about 30% w/w, at least one dissolution modifying excipient from about 5 to about 70% w/w selected from the group consisting of a swellable solid, a disintegrant, a non-reducing sugar, and a water soluble filler, and a combination or mixture thereof, and optionally a optionally a plasticizer from about 0 to 5% w/w, and/or a processing agent from about 0 to about 10% w/w; and
b) introducing the composition of step (a) into a hot melt extruder at a temperature of about 50°C, and extruding the composition at a temperature of about 125°C to form the extruded pharmaceutically acceptable composition.

70. (Previously presented) The method according to Claim 69 wherein the Aminoalkyl Methacrylate Copolymer E is present in an amount of about 50 to about 90% w/w.

71. (Previously presented) The method according to Claim 69 wherein the lubricant is stearyl alcohol, glycerol monostearate (GMS), talc, magnesium stearate, silicon dioxide, amorphous silicic acid, or fumed silica; or combinations or mixtures thereof.

72. (Previously presented) The method according to Claim 71 wherein the lubricant is stearyl alcohol or glycerol monostearate.

73. (Previously presented The method according to Claim 72 wherein the lubricant is present in an amount of about 5 to about 15% w/w.

74. (Previously presented) The method according to Claim 73 the lubricant is stearyl alcohol and is present in an amount of about 10 to about 12% w/w.

75. (Previously presented) The method according to Claim 69 wherein the dissolution modifying excipient is poly(ethylene) oxide, ethyl cellulose, cellulose acetate phthalate, hydroxypropylmethyl cellulose (HPMC), lactose, Starch 1500, croscarmellose sodium, copovidone, or crospovidone (cross-linked polyvinyl pyrrolidone); [[and]] or combinations or mixtures thereof.

76. (Previously presented) The method according to Claim 75 wherein the dissolution modifying excipient is polyethylene oxide, lactose, HPMC or copovidone; or combinations or mixtures thereof.

77. (Previously presented) The method according to Claim 75 wherein the dissolution modifying agent is polyethylene oxide present in an amount of about 5 to about 30% w/w.

78. (Previously presented) The method according to Claim 76 wherein the polyethylene oxide is present in an amount of about 10 to about 20 % w/w.

79. (Previously presented) The method according to Claim 75 wherein the dissolution modifying agent is a combination of polyethylene oxide, and at least one of lactose, HPMC, or copovidone.

80. (Previously presented) The method according to Claim 79 which is a combination of polyethylene oxide and copovidone.

81. (Previously presented) The method according to Claim 80 wherein the polyethyleneoxide is present in an amount of about 10 to 20% w/w, and the copovidone is present in an amount of 5 to 35% w/w.

82. (Previously presented) The method according to Claim 1 wherein the plasticizer is triethyl citrate (TEC), tributyl citrate, acetyl triethyl citrate (ATEC), acetyl tributyl citrate (ATBC), dibutyl phthalate, dibutyl sebacate (DBS), diethyl phthalate, vinyl pyrrolidone glycol triacetate, polyethylene glycol, polyoxyethylene sorbitan monolaurate, propylene glycol, or castor oil; or combinations or mixtures thereof.

83. (Previously presented) The method according to Claim 69 wherein the processing agent is talc.

84. (Previously presented) The method according to Claim 83 wherein the talc is present in an amount of 5 to 10% w/w.

85. (Previously presented) The method according to Claim 83 wherein the processing agent is talc present in an amount of 5 to 10% w/w, and the lubricant is stearyl alcohol present in an amount of 10 to 12% w/w.

86. (Previously presented) The method according to Claim 69 which further comprises a surfactant.

87. (Previously presented) The method according to Claim 86 wherein the surfactant is a block copolymers of ethylene oxide and propylene oxide, lecithin, sodium dioctyl sulfosuccinate, sodium lauryl sulfate, hydrogenated castor oil, polyoxyethylene sorbitan fatty acid esters, the sorbitan fatty acid esters, polyethylene glycol, glyceryl monostearate, d-alpha-tocopheryl polyethylene glycol 1000 succinate, sucrose fatty acid esters; or combinations or mixtures thereof.

88. (Previously presented) The method according to Claim 87 wherein the surfactant is a block copolymer of ethylene oxide and propylene oxide.

89. (Previously presented) The method according to Claim 87 wherein the surfactant is present in an amount of about 0.25 to 5% w/w.

90. (Previously presented) A method for making an injection molded pharmaceutically acceptable component comprising:

a) mixing aminoalkyl methacrylate copolymer E present in an amount of about 30 to about 90% w/w; a lubricant from about 0 to about 30% w/w, at least one dissolution modifying excipient from about 5 to about 70% w/w, and optionally a optionally a plasticizer from about 0 to 5% w/w, and/or a processing agent from about 0 to about 10% w/w; and

b) providing the composition of step (a) into a hot melt extruder to form an extrudate at a temperature less than or equal to about 125°C; and

c) providing the extrudate into an injection mold to form an injection molded pharmaceutically acceptable component.

91. (Previously presented) The method according to Claim 90 wherein the aminoalkyl methacrylate copolymer E is present in an amount of about 50 to about 90% w/w.

92. (Previously presented) The method according to Claim 90 wherein the lubricant is stearyl alcohol, glycerol monostearate (GMS), talc, magnesium stearate, silicon dioxide, amorphous silicic acid, or fumed silica; or combinations or mixtures thereof.

93. (Previously presented) The method according to Claim 92 wherein the lubricant is stearyl alcohol or glycerol monostearate.

94. (Previously presented) The method according to Claim 93 wherein the lubricant is present in an amount of about 5 to about 15% w/w.

95. (Previously presented) The method according to Claim 93 the lubricant is stearyl alcohol and is present in an amount of about 10 to about 12% w/w.

96. (Previously presented) The method according to Claim 90 wherein the dissolution modifying excipient is poly(ethylene) oxide, ethyl cellulose, cellulose acetate phthalate, hydroxypropylmethyl cellulose (HPMC), lactose, Starch 1500, croscarmellose sodium,

copovidone, or crospovidone (cross-linked polyvinyl pyrrolidone); or combinations or mixtures thereof.

97. (Previously presented) The method according to Claim 96 wherein the dissolution modifying excipient is polyethylene oxide, lactose, HPMC or copovidone; or combinations or mixtures thereof.

98. (Previously presented) The method according to Claim 96 wherein the dissolution modifying agent is polyethylene oxide present in an amount of about 5 to about 30% w/w.

99. (Previously presented) The method according to Claim 98 wherein the polyethylene oxide is present in an amount of about 10 to about 20 % w/w.

100. (Previously presented) The method according to Claim 96 wherein the dissolution modifying agent is a combination of polyethylene oxide, and at least one of lactose, HPMC, or copovidone.

101. (Previously presented) The method according to Claim 100 which is a combination of polyethylene oxide and copovidone.

102. (Previously presented) The method according to Claim 101 wherein the polyethyleneoxide is present in an amount of about 10 to 20% w/w, and the copovidone is present in an amount of 5 to 35% w/w.

103. (Previously presented) The method according to Claim 90 wherein the plasticizer is triethyl citrate (TEC), tributyl citrate, acetyl triethyl citrate (ATEC), acetyl tributyl citrate (ATBC), dibutyl phthalate, dibutyl sebacate (DBS), diethyl phthalate, vinyl pyrrolidone glycol triacetate, polyethylene glycol, polyoxyethylene sorbitan monolaurate, propylene glycol, or castor oil; or combinations or mixtures thereof.

104. (Previously presented) The method according to Claim 90 wherein the processing agent is talc.

105. (Previously presented) The method according to Claim 104 wherein the talc is present in an amount of 5 to 10% w/w.

106. (Previously presented) The method according to Claim 90 wherein the processing agent is talc present in an amount of 5 to 10% w/w, and the lubricant is stearyl alcohol present in an amount of 10 to 12% w/w.

107. (Previously presented) The method according to Claim 90 which further comprises a surfactant.

108. (Previously presented) The method according to Claim 107 wherein the surfactant is a block copolymers of ethylene oxide and propylene oxide, lecithin, sodium dioctyl sulfosuccinate, sodium lauryl sulfate, hydrogenated castor oil, polyoxyethylene sorbitan fatty acid esters, the sorbitan fatty acid esters, polyethylene glycol, glyceryl monostearate, d-alpha-tocopheryl polyethylene glycol 1000 succinate, sucrose fatty acid esters; or combinations and mixtures thereof.

109. (Previously presented) The method according to Claim 108 wherein the surfactant is a block copolymer of ethylene oxide and propylene oxide.

110. (Previously presented) The method according to Claim 108 wherein the surfactant is present in an amount of about 0.25 to 5% w/w.

111. (Withdrawn) The multi-component dosage form of claim 29, wherein the dissolution-modifying excipient is present in an amount of about 10 to about 30% w/w.

112. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 29 wherein the solid matrix polymeric composition comprises a copolymer of methyl acrylate,

methyl methacrylate and methacrylic acid, with molar ratio of monomer units of 7:3:1, present in an amount of about 73% w/w, hydroxypropylmethylcellulose present in an amount of about 10% w/w, lactose present in an amount of about 5.0% w/w, and stearyl alcohol present in an amount of about 12% w/w.

113. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 39, in which the lubricant is stearyl alcohol, present in an amount of about 10 to 12% w/w.

114. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 33, in which the lubricant is stearyl alcohol, present in an amount of about 10 to 12% w/w.

115. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29 wherein the dissolution modifying excipient is a swellable solid selected from poly(ethylene) oxide, hydroxypropyl cellulose (HPC), or hydroxypropylmethyl cellulose (HPMC), or a combination thereof, and wherein the swellable solid is present in an amount of about 5% to about 60% w/w.

116. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29 wherein the dissolution modifying excipient is poly(ethylene) oxide, ethyl cellulose, cellulose acetate phthalate, hydroxypropylmethyl cellulose (HPMC), hydroxypropylcellulose (HPC), lactose, Starch 1500, croscarmellose sodium, copovidone, or crospovidone (cross-linked polyvinyl pyrrolidone); or combinations or mixtures thereof.

117. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29 wherein the dissolution modifying excipient is a disintegrant selected from sodium starch glycollate, crospovidone or copovidone, present in an about of about 5% to 50% w/w.

118. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29 wherein the dissolution modifying excipient is a swellable solid, the lubricant is stearyl alcohol, and optionally contains a plasticizer and/or a processing aid.

119. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29 wherein the dissolution modifying excipient is polyethylene oxide, lactose, HPMC, hydroxypropylcellulose (HPC), or copovidone; or combinations or mixtures thereof.

120. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29 wherein the at least one dissolution modifying excipient is a disintegrant selected from the group consisting of sodium starch glycollate, crospovidone and copovidone, present in an about of about 5% to 50% w/w; a non-reducing sugar selected from the group consisting of xylitol and mannitol, present in the range of about 2.5 to 15% w/w; a water soluble filler present in the range of about 5 to 20% w/w; a swellable solid selected from the group consisting of poly(ethylene)oxide, hydroxypropylcellulose and hydroxypropylmethylcellulose, present in the range of about 5% w/w to 60% w/w; and combinations or mixtures thereof.

121. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 120 wherein the dissolution modifying agent is polyethylene oxide present in an amount of about 5 to 30% w/w.

122. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29 which the at least one dissolution modifying excipient is a disintegrant, and optionally contains a second dissolution modifying excipient which is a non-reducing sugar.

123. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 120 wherein the disintegrant is crospovidone (cross-linked polyvinyl pyrrolidone), or copovidone, or a mixture thereof.

124. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29 wherein the capsule composition comprises Aminoalkyl Methacrylate Copolymer E present in an amount of about 30 to 60% w/w, stearyl alcohol present in an amount from about 10 to 12% w/w, polyethylene oxide present in an amount of about 10 to 20% w/w, talc present in an amount from about 0 to 10% w/w, and copovidone present in an amount of about 0 to 35 %w/w.

125. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 124 wherein the Aminoalkyl Methacrylate Copolymer E is present in an amount of about 55% w/w, stearyl alcohol is present in an amount of about 10% w/w, copovidone present in an amount of about 5%, polyethylene oxide present in an amount of about 20% w/w and talc present in an amount of about 10% w/w.

126. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 124 wherein the Aminoalkyl Methacrylate Copolymer E present in an amount of about 60% w/w, stearyl alcohol is present in an amount of about 10% w/w, polyethylene oxide present in an amount of about 20% w/w and talc present in an amount of about 10% w/w.

127. (Previously presented) The method according to Claim 69 wherein the lubricant is present in an amount of about 5 to about 15% w/w.

128. (Previously presented) The method according to Claim 127 the lubricant is stearyl alcohol and is present in an amount of about 10 to about 12% w/w.

Remarks:

Claims 29, 31-45, 47-61, and 69-128 are currently pending.

The Examiner has made Claims 29, 31-45, 47-61, and 69-128 the subject of a restriction requirement as shown below:

Group I, claims 29, 31 to 45, 47, and 111 to 128, drawn to a multicomponent pharmaceutical dosage form

Group II, claims 47 to 61 drawn to a process for making a pharmaceutical dosage form comprising making a strand of ingredients and cutting that strand into pellets and then introducing those pellets into an injection molder and forming thin walled capsule compartments

Group III, claims 69-110, drawn to a method for making an extruded pharmaceutical composition be mixing the composition into a hot melt extruder at a certain temperature range.

It is believed that the Examiner has incorrectly included claims in Group I which are the subject matter of Group III. Group I presently includes claims 47, 127 and 128. Claim 47 is the main process claim of Group II, and Claims 127 and 128 stem from Claim 69 which is a process/method claim. Correction of the restriction is requested.

Applicants elect the process of Group II with traverse. The claims of Group III are also drawn to vastly similar process steps, the primary difference being the last steps of directly introducing the composition into the extruder without cutting the extruded strand into pellets. Consequently it is believed that both Group II and Group III should be examined together. No additional burden is placed upon the Examiner for such examination.

The multicomponent dosage form, e.g. the article of manufacture and its process are all inventions derived from a common research and development effort. Further, the original 11a US filing of this application has already been subject to a restriction which resulted in the instant claims of this 371 national case being directed to those groups. More importantly, this application is already an RCE of an application that has already had a number of office actions with claims directed to all of the above claims having been examined. Consequently it is not believed that the USPTO has had any additional burden placed upon it for continued examination

of these same claims. However, to advance prosecution claims 29, 31 to 45, 47, and 111 to 128 remain in the application but are noted herein as being withdrawn from consideration.

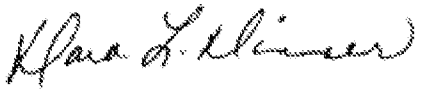
It should further be noted that this is still an application under the inventive concept of PCT Rule 13.1. All of the instant claims, including the single component dosage forms were searched and examined under the PCT application.

An election of a single disclosed species is requested, see page 3, 1rst full ¶ Office Action. Applicants elect the composition of Example 2, page 37 of the specification, e.g. 75% w/w E100, 5% w/w stearyl alcohol, and 20% w/w PolyOx N80.

All the claims in Group II read upon the elected species. All of the claims in Group I, but for Claims 42, 45, 117, and 123-126 also read upon this election.

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. If any additional fees or charges are required by this paper the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,



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Confirmation No.: 8632

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant: Mc Allister et al.
Serial No.: 10/470,439
Filed: 20 January 2004
For: PHARMACEUTICAL FORMULATION

17 March 2009
Group Art Unit No.: 1618
Examiner: J. W. Rogers

Commissioner for Patents
P.O. Box 1450
Arlington, VA 22313-1450

RESTRICTION & AMENDMENT

Sir:

Applicants now respond to the Office Action of 17 February 2009 for which entry of the following Remarks and Amendments into the record is respectfully requested.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks begin on page 17 of this paper.

Amendments to the Claims:

This listing of claims will replace all prior versions, and listings, of the claims in the application:

1 to 28 (Cancelled).

29. (Withdrawn) A multi-component pharmaceutical dosage form which comprises at least two sub-units, each sub-unit being selected from:

a) an extruded and injection molded capsule shell having an outer surface and an opposed inner surface, the shell comprising a blend of:

aminoalkyl methacrylate copolymer E present in an amount of about 50 to 90% w/w;

a lubricant from about 0 to about 30% w/w;

at least one dissolution-modifying excipient present in an amount from about 5 to 70% w/w and being selected from the group consisting of a swellable solid, a disintegrant, a non-reducing sugar, a water soluble filler, and a combination or mixture thereof; and

optionally a plasticizer from about 0 to 5% w/w and/or a processing agent from about 0 to 10% w/w;

the inner surface of the shell defining, at least in part, a confined space for containing a drug substance;

wherein the shell is soluble or disintegrable in a patient's gastro-intestinal environment for release of the drug substance contained in the shell;

and at least one of:

b) a solid matrix being comprised of a polymeric composition comprising a drug substance, the polymeric composition being soluble, dispersible or disintegrable in a patient's

gastro-intestinal environment for release of the drug substance contained in the solid matrix; or

c) a solid generally cylindrical linker body having an outer surface, the outer surface being exposed to the patient's gastro-intestinal environment, the cylindrical linker body being composed of an extruded material comprising a pharmaceutical composition which is soluble, dispersible or disintegrable in the patient's gastro-intestinal environment;

and in which, at least prior to administration to a patient, the at least two sub-units are assembled together into a dosage form.

30.(cancelled)

31. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29, in which the lubricant is present in an amount up to about 15% w/w.

32. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 31, in which the lubricant is stearyl alcohol and/or glyceryl monostearate.

33. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29, in which the lubricant is selected from the group consisting of stearyl alcohol, glycerol monostearate (GMS), talc, magnesium stearate, silicon dioxide, amorphous silicic acid, and fumed silica; and combinations or mixtures thereof.

34. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29 in which the processing agent is talc.

35. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29, in which the dissolution-modifying excipient of the shell is polyethylene oxide.

36. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29, in which the dissolution-modifying excipient of the shell is a combination of polyethyleneoxide, talc, Starch 1500, lactose, hydroxypropylmethyl-cellulose, or co-povidone.

37. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 36, in which the lubricant is stearyl alcohol.

38. (Withdrawn) A dosage form according to Claim 29, comprising a plurality of drug substance-containing sub-units, wherein at least one sub-unit comprises the extruded and injection molded shell made of a pharmaceutically acceptable polymeric composition comprising Aminoalkyl Methacrylate Copolymer E present in an amount of about 50 to 90% w/w, and a dissolution-modifying excipient present in an amount of about 10 to about 30% w/w; and at least one of the solid matrix sub-unit or the linker body sub-unit is composed of polymeric composition comprising a copolymer of methacrylic acid, methyl acrylate and methyl methacrylate with a molar ratio of the monomer units of 7:3:1.

39. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 38, in which the Aminoalkyl Methacrylate Copolymer E is present in an amount of about 30 to 90% w/w, and-the lubricant is selected from the group consisting of stearyl alcohol, glycerol monostearate (GMS), talc, magnesium stearate, silicon dioxide, amorphous silicic acid, and fumed silica; and combinations or mixtures thereof.

40. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 39, in which the lubricant is present in an amount up to about 15% w/w.

41. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 39, in which the lubricant is present in an amount of about 5 to 15% w/w.

42. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 39, in which the polymeric composition further comprises a processing agent present in an amount up to about 10% w/w.

43. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29, in which at least one of the sub-units is a drug substance-containing capsule compartment

having a wall with a thickness in the range of about 0.3 – 0.8 mm.

44. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29, in which at least one of the sub-units releases the drug substance as a substantially immediate release.

45. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29, in which at least one of the sub-units releases the drug substance as a sustained release or pulsed release.

46.(cancelled)

47. (Previously presented) A process for making a pharmaceutical dosage form comprising the steps of:

a) introducing Aminoalkyl Methacrylate Copolymer E present in an amount of about 50 to 90% w/w and an excipient composition comprising at least one dissolution-modifying excipient present in an amount from about 5 to 70% w/w selected from the group consisting of a swellable solid, a disintegrant, a non-reducing sugar, and a water soluble filler, and combinations or mixtures thereof, and a lubricant present in an amount up to about 15% w/w, simultaneously into a first location of an elongated hot melt extruder, the first location having a temperature of about 50°C;

b) mixing said Aminoalkyl Methacrylate Copolymer E and said excipient composition in the hot melt extruder at a temperature ranging from about 50°C to about 125°C to form a homogeneous composition therein and substantially without thermal degradation of the Aminoalkyl Methacrylate Copolymer E and the excipient composition;

(c) extruding the homogeneous composition in the form of a strand from the hot melt extruder though a die at a second location distal from said first location, said second location having a temperature not greater than about 125°C;

c) cutting the strand into pellets; and

d) introducing said pellets into an injection molder and forming thin-walled capsule compartments from said pellets by injection molding.

48. (Previously presented) The process according to Claim 47, wherein the dissolution modifying excipient is poly(ethylene) oxide, ethyl cellulose, cellulose acetate phthalate, hydroxypropylmethyl cellulose (HPMC), lactose, Starch 1500, croscarmellose sodium, copovidone, or crospovidone (cross-linked polyvinyl pyrrolidone); or combinations or mixtures thereof.

49. (Previously presented) The process according to Claim 48, wherein the dissolution modifying excipient is polyethylene oxide.

50. (Previously presented) The process according to Claim 47 wherein the lubricant is stearyl alcohol, glycerol monostearate (GMS), talc, magnesium stearate, silicon dioxide, amorphous silicic acid, or fumed silica; or combinations or mixtures thereof.

51. (Previously presented) The process according to Claim 47, in which the hot melt extruder is maintained at a temperature not exceeding approximately 120°C.

52. (previously presented) The process according to Claim 47, in which the hot melt extruder is maintained at a temperature not lower than the Aminoalkyl Methacrylate Copolymer E and said excipient composition melting points.

53. (Previously presented) The process according to Claim 47, in which the temperature in the hot melt extruder gradually increases along the length of the hot melt extruder, from said first location at which the Aminoalkyl Methacrylate Copolymer E and an excipient composition are introduced, to the die, the maximum temperature not exceeding approximately 125°C.

54. (Previously presented) The process according to Claim 47, in which the hot melt extruder comprises an elongated barrel having first and second opposite ends, and twin screws within the barrel for propelling Aminoalkyl Methacrylate Copolymer E and said excipient composition along the length of the interior of the barrel, said first location at which the

Aminoalkyl Methacrylate Copolymer E and said excipient composition are introduced being located adjacent the first end of the barrel, and said die being located adjacent the second end of the barrel.

55. (Previously presented) The process according to Claim 47, in which the injection molding of the thin-walled capsule compartments is carried out using an injection molder having a barrel and a nozzle, while maintaining the injection molder barrel at a temperature in the range of about 110°C to 130°C.

56. (Previously presented) The process according to Claim 47, in which the injection molding of the thin-walled capsule compartments is carried out using an injection molder having a barrel and a nozzle, while maintaining the injection molder nozzle at a temperature in the range of about 130°C to 150°C.

57. (Previously presented) The process according to Claim 47, in which the injection molding of the thin-walled capsule compartments is carried out using an injection molder having a barrel and a nozzle, while maintaining the injection molder nozzle at a temperature of about 140°C.

58. (Previously presented) The process according to Claim 47, in which the injection molding of the thin-walled capsule compartments is carried out using an injection molder having a barrel and a nozzle, while maintaining the injection molder barrel at a temperature in the range of about 110°C to 130°C and maintaining the injection molder nozzle at a temperature in the range of about 130°C to 150°C.

59. (original) The process according to Claim 47 wherein the pharmaceutical dosage forms are assembled using said capsule compartments as components of said dosage forms.

60. (original) The process according to Claim 59 wherein the said capsule compartments of the assembled dosage form are connected together by at least one weld where adjacent parts of said components are in contact.

61. (original) The process according to Claim 60 wherein the weld is produced by a thermal weld, an ultrasonic weld, an inductive weld, or an adhesive weld.

62 – 68 (cancelled).

69. (Previously presented) A method for making an extruded pharmaceutically acceptable composition comprising:

a) mixing Aminoalkyl Methacrylate Copolymer E present in an amount of about 30 to 90% w/w; a lubricant from about 0 to about 30% w/w, at least one dissolution modifying excipient from about 5 to about 70% w/w selected from the group consisting of a swellable solid, a disintegrant, a non-reducing sugar, and a water soluble filler, and a combination or mixture thereof, and optionally a optionally a plasticizer from about 0 to 5% w/w, and/or a processing agent from about 0 to about 10% w/w; and
b) introducing the composition of step (a) into a hot melt extruder at a temperature of about 50°C, and extruding the composition at a temperature of about 125°C to form the extruded pharmaceutically acceptable composition.

70. (Previously presented) The method according to Claim 69 wherein the Aminoalkyl Methacrylate Copolymer E is present in an amount of about 50 to about 90% w/w.

71. (Previously presented) The method according to Claim 69 wherein the lubricant is stearyl alcohol, glycerol monostearate (GMS), talc, magnesium stearate, silicon dioxide, amorphous silicic acid, or fumed silica; or combinations or mixtures thereof.

72. (Previously presented) The method according to Claim 71 wherein the lubricant is stearyl alcohol or glycerol monostearate.

73. (Previously presented The method according to Claim 72 wherein the lubricant is present in an amount of about 5 to about 15% w/w.

74. (Previously presented) The method according to Claim 73 the lubricant is stearyl alcohol and is present in an amount of about 10 to about 12% w/w.

75. (Previously presented) The method according to Claim 69 wherein the dissolution modifying excipient is poly(ethylene) oxide, ethyl cellulose, cellulose acetate phthalate, hydroxypropylmethyl cellulose (HPMC), lactose, Starch 1500, croscarmellose sodium, copovidone, or crospovidone (cross-linked polyvinyl pyrrolidone); [[and]] or combinations or mixtures thereof.

76. (Previously presented) The method according to Claim 75 wherein the dissolution modifying excipient is polyethylene oxide, lactose, HPMC or copovidone; or combinations or mixtures thereof.

77. (Previously presented) The method according to Claim 75 wherein the dissolution modifying agent is polyethylene oxide present in an amount of about 5 to about 30% w/w.

78. (Previously presented) The method according to Claim 76 wherein the polyethylene oxide is present in an amount of about 10 to about 20 % w/w.

79. (Previously presented) The method according to Claim 75 wherein the dissolution modifying agent is a combination of polyethylene oxide, and at least one of lactose, HPMC, or copovidone.

80. (Previously presented) The method according to Claim 79 which is a combination of polyethylene oxide and copovidone.

81. (Previously presented) The method according to Claim 80 wherein the polyethyleneoxide is present in an amount of about 10 to 20% w/w, and the copovidone is present in an amount of 5 to 35% w/w.

82. (Previously presented) The method according to Claim 1 wherein the plasticizer is triethyl citrate (TEC), tributyl citrate, acetyl triethyl citrate (ATEC), acetyl tributyl citrate (ATBC), dibutyl phthalate, dibutyl sebacate (DBS), diethyl phthalate, vinyl pyrrolidone glycol triacetate, polyethylene glycol, polyoxyethylene sorbitan monolaurate, propylene glycol, or castor oil; or combinations or mixtures thereof.

83. (Previously presented) The method according to Claim 69 wherein the processing agent is talc.

84. (Previously presented) The method according to Claim 83 wherein the talc is present in an amount of 5 to 10% w/w.

85. (Previously presented) The method according to Claim 83 wherein the processing agent is talc present in an amount of 5 to 10% w/w, and the lubricant is stearyl alcohol present in an amount of 10 to 12% w/w.

86. (Previously presented) The method according to Claim 69 which further comprises a surfactant.

87. (Previously presented) The method according to Claim 86 wherein the surfactant is a block copolymers of ethylene oxide and propylene oxide, lecithin, sodium dioctyl sulfosuccinate, sodium lauryl sulfate, hydrogenated castor oil, polyoxyethylene sorbitan fatty acid esters, the sorbitan fatty acid esters, polyethylene glycol, glyceryl monostearate, d-alpha-tocopheryl polyethylene glycol 1000 succinate, sucrose fatty acid esters; or combinations or mixtures thereof.

88. (Previously presented) The method according to Claim 87 wherein the surfactant is a block copolymer of ethylene oxide and propylene oxide.

89. (Previously presented) The method according to Claim 87 wherein the surfactant is present in an amount of about 0.25 to 5% w/w.

90. (Previously presented) A method for making an injection molded pharmaceutically acceptable component comprising:

a) mixing aminoalkyl methacrylate copolymer E present in an amount of about 30 to about 90% w/w; a lubricant from about 0 to about 30% w/w, at least one dissolution modifying excipient from about 5 to about 70% w/w, and optionally a optionally a plasticizer from about 0 to 5% w/w, and/or a processing agent from about 0 to about 10% w/w; and

b) providing the composition of step (a) into a hot melt extruder to form an extrudate at a temperature less than or equal to about 125°C; and

c) providing the extrudate into an injection mold to form an injection molded pharmaceutically acceptable component.

91. (Previously presented) The method according to Claim 90 wherein the aminoalkyl methacrylate copolymer E is present in an amount of about 50 to about 90% w/w.

92. (Previously presented) The method according to Claim 90 wherein the lubricant is stearyl alcohol, glycerol monostearate (GMS), talc, magnesium stearate, silicon dioxide, amorphous silicic acid, or fumed silica; or combinations or mixtures thereof.

93. (Previously presented) The method according to Claim 92 wherein the lubricant is stearyl alcohol or glycerol monostearate.

94. (Previously presented) The method according to Claim 93 wherein the lubricant is present in an amount of about 5 to about 15% w/w.

95. (Previously presented) The method according to Claim 93 the lubricant is stearyl alcohol and is present in an amount of about 10 to about 12% w/w.

96. (Previously presented) The method according to Claim 90 wherein the dissolution modifying excipient is poly(ethylene) oxide, ethyl cellulose, cellulose acetate phthalate, hydroxypropylmethyl cellulose (HPMC), lactose, Starch 1500, croscarmellose sodium,

copovidone, or crospovidone (cross-linked polyvinyl pyrrolidone); or combinations or mixtures thereof.

97. (Previously presented) The method according to Claim 96 wherein the dissolution modifying excipient is polyethylene oxide, lactose, HPMC or copovidone; or combinations or mixtures thereof.

98. (Previously presented) The method according to Claim 96 wherein the dissolution modifying agent is polyethylene oxide present in an amount of about 5 to about 30% w/w.

99. (Previously presented) The method according to Claim 98 wherein the polyethylene oxide is present in an amount of about 10 to about 20 % w/w.

100. (Previously presented) The method according to Claim 96 wherein the dissolution modifying agent is a combination of polyethylene oxide, and at least one of lactose, HPMC, or copovidone.

101. (Previously presented) The method according to Claim 100 which is a combination of polyethylene oxide and copovidone.

102. (Previously presented) The method according to Claim 101 wherein the polyethyleneoxide is present in an amount of about 10 to 20% w/w, and the copovidone is present in an amount of 5 to 35% w/w.

103. (Previously presented) The method according to Claim 90 wherein the plasticizer is triethyl citrate (TEC), tributyl citrate, acetyl triethyl citrate (ATEC), acetyl tributyl citrate (ATBC), dibutyl phthalate, dibutyl sebacate (DBS), diethyl phthalate, vinyl pyrrolidone glycol triacetate, polyethylene glycol, polyoxyethylene sorbitan monolaurate, propylene glycol, or castor oil; or combinations or mixtures thereof.

104. (Previously presented) The method according to Claim 90 wherein the processing agent is talc.

105. (Previously presented) The method according to Claim 104 wherein the talc is present in an amount of 5 to 10% w/w.

106. (Previously presented) The method according to Claim 90 wherein the processing agent is talc present in an amount of 5 to 10% w/w, and the lubricant is stearyl alcohol present in an amount of 10 to 12% w/w.

107. (Previously presented) The method according to Claim 90 which further comprises a surfactant.

108. (Previously presented) The method according to Claim 107 wherein the surfactant is a block copolymers of ethylene oxide and propylene oxide, lecithin, sodium dioctyl sulfosuccinate, sodium lauryl sulfate, hydrogenated castor oil, polyoxyethylene sorbitan fatty acid esters, the sorbitan fatty acid esters, polyethylene glycol, glyceryl monostearate, d-alpha-tocopheryl polyethylene glycol 1000 succinate, sucrose fatty acid esters; or combinations and mixtures thereof.

109. (Previously presented) The method according to Claim 108 wherein the surfactant is a block copolymer of ethylene oxide and propylene oxide.

110. (Previously presented) The method according to Claim 108 wherein the surfactant is present in an amount of about 0.25 to 5% w/w.

111. (Withdrawn) The multi-component dosage form of claim 29, wherein the dissolution-modifying excipient is present in an amount of about 10 to about 30% w/w.

112. (Withdrawn) The multi-component pharmaceutical dosage form according to Claim 29 wherein the solid matrix polymeric composition comprises a copolymer of methyl acrylate,

methyl methacrylate and methacrylic acid, with molar ratio of monomer units of 7:3:1, present in an amount of about 73% w/w, hydroxypropylmethylcellulose present in an amount of about 10% w/w, lactose present in an amount of about 5.0% w/w, and stearyl alcohol present in an amount of about 12% w/w.

113. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 39, in which the lubricant is stearyl alcohol, present in an amount of about 10 to 12% w/w.

114. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 33, in which the lubricant is stearyl alcohol, present in an amount of about 10 to 12% w/w.

115. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29 wherein the dissolution modifying excipient is a swellable solid selected from poly(ethylene) oxide, hydroxypropyl cellulose (HPC), or hydroxypropylmethyl cellulose (HPMC), or a combination thereof, and wherein the swellable solid is present in an amount of about 5% to about 60% w/w.

116. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29 wherein the dissolution modifying excipient is poly(ethylene) oxide, ethyl cellulose, cellulose acetate phthalate, hydroxypropylmethyl cellulose (HPMC), hydroxypropylcellulose (HPC), lactose, Starch 1500, croscarmellose sodium, copovidone, or crospovidone (cross-linked polyvinyl pyrrolidone); or combinations or mixtures thereof.

117. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29 wherein the dissolution modifying excipient is a disintegrant selected from sodium starch glycollate, crospovidone or copovidone, present in an about of about 5% to 50% w/w.

118. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29 wherein the dissolution modifying excipient is a swellable solid, the lubricant is stearyl alcohol, and optionally contains a plasticizer and/or a processing aid.

119. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29 wherein the dissolution modifying excipient is polyethylene oxide, lactose, HPMC, hydroxypropylcellulose (HPC), or copovidone; or combinations or mixtures thereof.

120. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29 wherein the at least one dissolution modifying excipient is a disintegrant selected from the group consisting of sodium starch glycollate, crospovidone and copovidone, present in an about of about 5% to 50% w/w; a non-reducing sugar selected from the group consisting of xylitol and mannitol, present in the range of about 2.5 to 15% w/w; a water soluble filler present in the range of about 5 to 20% w/w; a swellable solid selected from the group consisting of poly(ethylene)oxide, hydroxypropylcellulose and hydroxypropylmethylcellulose, present in the range of about 5% w/w to 60% w/w; and combinations or mixtures thereof.

121. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 120 wherein the dissolution modifying agent is polyethylene oxide present in an amount of about 5 to 30% w/w.

122. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29 which the at least one dissolution modifying excipient is a disintegrant, and optionally contains a second dissolution modifying excipient which is a non-reducing sugar.

123. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 120 wherein the disintegrant is crospovidone (cross-linked polyvinyl pyrrolidone), or copovidone, or a mixture thereof.

124. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 29 wherein the capsule composition comprises Aminoalkyl Methacrylate Copolymer E present in an amount of about 30 to 60% w/w, stearyl alcohol present in an amount from about 10 to 12% w/w, polyethylene oxide present in an amount of about 10 to 20% w/w, talc present in an amount from about 0 to 10% w/w, and copovidone present in an amount of about 0 to 35 %w/w.

125. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 124 wherein the Aminoalkyl Methacrylate Copolymer E is present in an amount of about 55% w/w, stearyl alcohol is present in an amount of about 10% w/w, copovidone present in an amount of about 5%, polyethylene oxide present in an amount of about 20% w/w and talc present in an amount of about 10% w/w.

126. (Withdrawn) A multi-component pharmaceutical dosage form according to Claim 124 wherein the Aminoalkyl Methacrylate Copolymer E present in an amount of about 60% w/w, stearyl alcohol is present in an amount of about 10% w/w, polyethylene oxide present in an amount of about 20% w/w and talc present in an amount of about 10% w/w.

127. (Previously presented) The method according to Claim 69 wherein the lubricant is present in an amount of about 5 to about 15% w/w.

128. (Previously presented) The method according to Claim 127 the lubricant is stearyl alcohol and is present in an amount of about 10 to about 12% w/w.

Remarks:

Claims 29, 31-45, 47-61, and 69-128 are currently pending.

The Examiner has made Claims 29, 31-45, 47-61, and 69-128 the subject of a restriction requirement as shown below:

Group I, claims 29, 31 to 45, 47, and 111 to 128, drawn to a multicomponent pharmaceutical dosage form

Group II, claims 47 to 61 drawn to a process for making a pharmaceutical dosage form comprising making a strand of ingredients and cutting that strand into pellets and then introducing those pellets into an injection molder and forming thin walled capsule compartments

Group III, claims 69-110, drawn to a method for making an extruded pharmaceutical composition be mixing the composition into a hot melt extruder at a certain temperature range.

It is believed that the Examiner has incorrectly included claims in Group I which are the subject matter of Group III. Group I presently includes claims 47, 127 and 128. Claim 47 is the main process claim of Group II, and Claims 127 and 128 stem from Claim 69 which is a process/method claim. Correction of the restriction is requested.

Applicants elect the process of Group II with traverse. The claims of Group III are also drawn to vastly similar process steps, the primary difference being the last steps of directly introducing the composition into the extruder without cutting the extruded strand into pellets. Consequently it is believed that both Group II and Group III should be examined together. No additional burden is placed upon the Examiner for such examination.

The multicomponent dosage form, e.g. the article of manufacture and its process are all inventions derived from a common research and development effort. Further, the original 11a US filing of this application has already been subject to a restriction which resulted in the instant claims of this 371 national case being directed to those groups. More importantly, this application is already an RCE of an application that has already had a number of office actions with claims directed to all of the above claims having been examined. Consequently it is not believed that the USPTO has had any additional burden placed upon it for continued examination

of these same claims. However, to advance prosecution claims 29, 31 to 45, 47, and 111 to 128 remain in the application but are noted herein as being withdrawn from consideration.

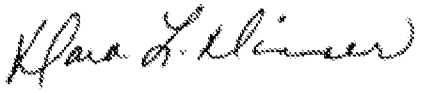
It should further be noted that this is still an application under the inventive concept of PCT Rule 13.1. All of the instant claims, including the single component dosage forms were searched and examined under the PCT application.

An election of a single disclosed species is requested, see page 3, 1rst full ¶ Office Action. Applicants elect the composition of Example 2, page 37 of the specification, e.g. 75% w/w E100, 5% w/w stearyl alcohol, and 20% w/w PolyOx N80.

All the claims in Group II read upon the elected species. All of the claims in Group I, but for Claims 42, 45, 117, and 123-126 also read upon this election.

Should the Examiner have any questions or wish to discuss any aspect of this case, the Examiner is encouraged to call the undersigned at the number below. If any additional fees or charges are required by this paper the Commissioner is hereby authorized to charge Deposit account 19-2570 accordingly.

Respectfully submitted,



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